



Caractérisation et traitement du substrat électrique pour la thérapie de resynchronisation cardiaque

Sylvain Ploux

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Sylvain Ploux. Caractérisation et traitement du substrat électrique pour la thérapie de resynchronisation cardiaque. Biologie cellulaire. Université de Bordeaux, 2014. Français. NNT : 2014BORD0180 . tel-01165055

HAL Id: tel-01165055

<https://theses.hal.science/tel-01165055>

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THÈSE PRÉSENTÉE
POUR OBTENIR LE GRADE DE
DOCTEUR DE
L'UNIVERSITÉ DE BORDEAUX

SCIENCES DE LA VIE ET DE LA SANTÉ
BIOLOGIE CELLULAIRE ET PHYSIOPATHOLOGIE

Par Sylvain Ploux

**Caractérisation et traitement du substrat électrique pour la
thérapie de resynchronisation cardiaque**

Sous la direction de : Pierre Bordachar

Soutenue le 29 octobre 2014

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Caractérisation et traitement du substrat électrique pour la thérapie de resynchronisation cardiaque

L'objectif de ce travail était de mieux appréhender les mécanismes impliqués dans la réponse à la resynchronisation biventriculaire (BIV) en insistant sur la caractérisation du substrat électrique éligible à la thérapie et l'intérêt de la resynchronisation électrique. Nous avons démontré qu'il existe une relation forte entre l'asynchronisme électrique de base défini tant par l'ECG de surface que par cartographie détaillée de l'activation ventriculaire (ECM) et la réponse hémodynamique à la stimulation BIV. Par rapport à l'ECG de surface, l'ECM permet une caractérisation plus fine de l'asynchronisme électrique ventriculaire avec une meilleure prédiction de la réponse clinique à la stimulation BIV. La présence d'un asynchronisme de base minimum, en particulier d'un retard d'activation ventriculaire gauche (VG) par rapport au ventricule droit (typiquement >50ms), est un prérequis à l'efficacité de la thérapie. Les patients avec bloc de branche gauche présentent un haut degré d'asynchronisme et la stimulation BIV agit sur ce substrat par resynchronisation de l'activation électrique. A contrario, la stimulation BIV dégrade la séquence d'activation ainsi que l'hémodynamique des patients à QRS fins (dyssynchronie iatrogène). Les patients présentant un trouble de conduction aspécifique présentent des degrés variables d'asynchronie électrique et en conséquence des réponses contrastées à la stimulation BIV. De même, l'analyse ECM de l'asynchronisme des patients chroniquement stimulés sur le ventricule droit a permis de mettre en évidence des degrés variables de retard d'activation du VG. Si la resynchronisation électrique est garante d'une amélioration de la fonction cardiaque, d'autres mécanismes sont impliqués telle la redistribution du travail segmentaire au sein du myocarde ventriculaire. L'efficacité de la stimulation mono-VG implique une participation accrue du ventricule droit au travail global (interaction ventriculaire).

Mots clés : Thérapie de resynchronisation cardiaque. Asynchronisme cardiaque. Cartographie d'activation électrique. Insuffisance cardiaque. Modélisation cardiaque.

Characterization and treatment of the electrical substrate for cardiac resynchronization therapy

We aimed to characterize the electrical substrate amenable to biventricular pacing (BVP) and to assess the actual value of electrical resynchronization. We showed, both with respect to surface ECG and detailed ventricular electrocardiographic mapping (ECM), a strong relationship between the baseline electrical dyssynchrony and the hemodynamic response to BIV pacing. Compared with standard ECG, ECM allows a more detailed analysis of the ventricular dyssynchrony and better predicts clinical outcomes after BVP. A minimal amount of electrical dyssynchrony, in particular a sufficient LV activation delay relative to right ventricular activation, is a prerequisite to the hemodynamic response to BVP. Due to their advanced electrical dyssynchrony, patients with left bundle branch block present potential for BVP positive response which acts by electrical resynchronization. Conversely, BVP worsens the electrical activation (iatrogenic dyssynchrony) and hemodynamics in patients with narrow QRS suffering from insufficient electrical dyssynchrony at baseline. Patients with unspecified conduction disorders show variable levels of electrical dyssynchrony and as a consequence mixed results to BVP. Similarly, ECM reveals a variable degree of left ventricular activation delay in patients chronically paced in the right ventricle. Beside the electrical resynchronization, other mechanisms are involved in the cardiac pump function improvement such as the redistribution of the mechanical work over the right and left ventricles. Through ventricular interaction, the RV myocardium importantly contributes to the improvement in LV pump function induced by single site LV pacing.

Keywords : Cardiac resynchronization therapy ; Cardiac dyssynchrony ; Electrocardiographic Mapping ; Heart Failure, Cardiac modeling.

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A notre Directeur,

Mr le Pr Pierre Bordachar

Professeur des Universités Praticien hospitalier - CHU Bordeaux,

Les partitions présentées ici ne sont que quelques pièces de l'Opéra que tu composes. Merci de m'avoir associé à ton œuvre mon ami.

A notre Président,

Mr le Pr Jean-Claude Daubert,

Professeur des universités Praticien Hospitalier - CHU Rennes,

Merci de m'avoir fait l'honneur de présider cette thèse. Vous avez été à l'initiative de cette thérapie, de sa compréhension et de son rayonnement international. Vos élèves comptent parmi les stimulistes les plus brillants. L'un d'eux nous a rejoint, Philippe, vous êtes sa référence, il est la nôtre.

A notre Rapporteur,

Mr le Pr Christophe Leclercq,

Professeur des universités Praticien Hospitalier - CHU Rennes,

Merci d'avoir accepté de juger cette thèse dédiée à la resynchronisation cardiaque. Votre expertise dans ce domaine n'a pas d'équivalent. Merci de l'intérêt que vous portez à nos travaux.

A notre Rapporteur,

Mr Rémi Dubois,

MCU - École supérieure de physique et de chimie industrielles de la ville de Paris,

Merci d'avoir accepté de juger cette thèse. Merci au Liryc de nous donner l'opportunité de travailler avec des scientifiques de ta classe et de ton talent.

A notre Juge,

Mr le Pr Pierre Jaïs,

Professeur des Universités Praticien hospitalier - CHU Bordeaux,

Merci Pierre de me faire l'honneur de juger ce travail. Merci pour ton indéfectible soutien. Capacité d'innovation, intégrité et rigueur sont des valeurs que tu portes haut et qui nous inspirent.

A mes maitres qui ont rendu ce travail possible :

Pr. Michel Haïssaguerre,

Pr. Pierre Dos Santos,

Pr. Frits Prinzen,

A mes collègues et co-auteurs :

Dr Philippe Ritter,

Dr Adlane Zemmoura,

Pr Michel Montaudon,

Dr Méléze Hocini,

Dr Sana Amraoui,

Pr Laurent Barandon,

Dr Frédéric Sacher,

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Pr Darrel Francis,

Dr Romain Eschaliér,

Dr Lionel Leroux,

Pr Niraj Varma,

Dr Arnaud Denis,

Pr Olivier Bernus,

Pr Jacques Clementy

Merci à l'Unité INSERM 1045 et au Pr. Roger Marthan,

A l'équipe des ARC du service d'électrophysiologie et de stimulation cardiaque.

Aux membres du Liryc.

Merci à la Fédération Française de Cardiologie.

A Amélie ma femme, Augustin, Valentine et Théophile mes trésors.

A Pierrot et Chan mes parents, Vincent, Yann, Eymeric, Benjamin et Tristan mes frères.

Liste des publications présentées dans ce manuscrit :

Strik M, **Ploux S**, Vernooy K, Prinzen FW. Cardiac resynchronization therapy: refocus on the electrical substrate. *Circ J*. 2011;75(6):1297-304. Epub 2011 Apr 29. Review.

Ploux S, Whinnett Z, Lumens J, Denis A, Zemmoura A, De Guillebon M, Ramoul K, Ritter P, Jaïs P, Clementy J, Haïssaguerre M, Bordachar P. Acute hemodynamic response to biventricular pacing in heart failure patients with narrow, moderately, and severely prolonged QRS duration. *Heart Rhythm*. 2012 Aug;9(8):1247-50.

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Publications connexes :

Derval N, Bordachar P, Lim HS, Sacher F, **Ploux S**, Laborderie J, Steendijk P, Deplagne A, Ritter P, Garrigue S, Denis A, Hocini M, Haissaguerre M, Clementy J, Jaïs P. Impact of Pacing Site on QRS Duration and Its Relationship to Hemodynamic Response in Cardiac Resynchronization Therapy for Congestive Heart Failure. *J Cardiovasc Electrophysiol*. 2014 Sep;25(9):1012-20. doi: 10.1111/jce.12464.

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Table des Matières

INTRODUCTION

1	INSUFFISANCE CARDIAQUE, ASYNCHRONISME ET RESYNCHRONISATION	13
2	OBJECTIFS DE CE TRAVAIL	15
3	REFERENCES	17

MATERIELS & METHODES

4	RECONSTRUCTION NON INVASIVE DE L'ACTIVITE ELECTRIQUE CARDIAQUE	26
4.1	L'ELECTROCARDIOGRAMME 12 DERIVATIONS DE SURFACE	26
4.2	CARTOGRAPHIE DE POTENTIELS DE SURFACE, BSPM	27
4.3	IMAGERIE ELECTROCARDIOGRAPHIQUE, OU CARTOGRAPHIE D'ACTIVATION ELECTROCARDIOGRAPHIQUE NON INVASIVE- ELECTROCARDIOGRAPHIC MAPPING ECM.....	28
5	LA MODELISATION CARDIAQUE NUMERIQUE : CIRCAdapt MODEL.	35
6	REFERENCES	39

RESULTATS

7	IMPACT SUR LA dp/dt_{maxVG} DE LA STIMULATION BIVENTRICULAIRE CHEZ DES PATIENTS INSUFFISANTS CARDIAQUES PRESENTANT DES QRS FINS, MODEREMENT OU SEVEREMENT ELARGIS.*	48
7.1	INTRODUCTION:	48
7.2	RESULTATS :	49
8	LA CARTOGRAPHIE D'ACTIVATION NON INVASIVE ELECTROCARDIOGRAPHIQUE (ECM) POUR AMELIORER LA SELECTION DES CANDIDATS A LA CRT : AU-DELA DE LA DUREE DU QRS OU L'ASPECT DE BLOC DE BRANCHE GAUCHE.*	
8.1	INTRODUCTION:	50
8.2	RÉSULTATS:	51
8.2.1	Activation	51
8.2.2	Asynchronisme électrique et réponse	51

9	ANALYSE PAR CARTOGRAPHIE ELECTROCARDIOGRAPHIQUE DE L'ACTIVATION INDUITE PAR LA STIMULATION APICALE VENTRICULAIRE DROITE ET DE L'ACTIVATION DE BLOC DE BRANCHE GAUCHE : COMPARAISON ET IMPLICATION POUR LA THERAPIE DE RESYNCHRONISATION CARDIAQUE. *	53
9.1	INTRODUCTION	53
9.2	RESULTATS	53
10	EVALUATION DE L'ASYNCHRONISME ELECTRIQUE INDUIT PAR LA STIMULATION BIVENTRICULAIRE : IMPLICATIONS POUR LA SELECTION DES PATIENTS ET L'AMELIORATION DE LA THERAPIE. *	55
10.1	INTRODUCTION :	55
10.2	RESULTATS	56
10.2.1	Activation	56
10.2.2	Relation dyssynchronie/hémodynamique	56
10.2.3	Répondeurs vs nonrépondeurs	57
11	EFFETS HEMODYNAMIQUES ET ELECTRIQUES DE LA STIMULATION VENTRICULAIRE GAUCHE MULTIPOINTS SUR UN MODELE CANIN DE BLOC DE BRANCHE GAUCHE. *	59
11.1	INTRODUCTION	59
11.2	METHODE ET RESULTATS	60
11.3	3. CONCLUSION	61
12	ETUDE COMPARATIVE DES MODES DE STIMULATION MONO-VG ET BIV SUR DIFFERENTS MODELES D'INSUFFISANCE CARDIAQUE AVEC BBG. *	63
12.1	INTRODUCTION	63
12.2	METHODE ET RESULTATS	64
12.3	CONCLUSION	65
13	STIMULATION ENDOCARDIQUE VG ET STIMULATION MULTIPOINTS COMME NOUVELLES STRATEGIES POUR L'APPLICATION DE LA THERAPIE DE RESYNCHRONISATION CARDIAQUE. *, **	67
13.1	LA STIMULATION ENDOCARDIQUE VENTRICULAIRE GAUCHE	67
13.1.1	Rationnel	67

13.1.2	Aspects techniques	68
13.1.3	Niveau de preuve.....	68
13.1.4	Complications potentielles.....	69
13.1.5	Perspectives.....	70
13.2	LA STIMULATION MULTIPPOINTS	70
13.2.1	Rationnel	70
13.2.2	Aspects techniques	70
13.2.3	Niveau de preuve.....	70
13.2.4	Limites & perspectives	71
14	REFERENCES.....	72
 SYNTHESE & PERSPECTIVES		
15	SYNTHESE ET PERSPECTIVES	81
15.1	BLOC DE BRANCHE GAUCHE, DECOUPLAGE D'ACTIVATION VENTRICULAIRE, REPONSE FAVORABLE A LA RESYNCHRONISATION, MECANISMES IMPLIQUES	82
15.2	QRS FINS, NOTION DE DESYNCHRONISATION ET ASYNCHRONISME POST-« RESYNCHRONISATION »	83
15.3	BLOC INDIFFERENCIE.....	84
15.4	STIMULATION VENTRICULAIRE DROITE VERSUS BLOC DE BRANCHE GAUCHE	87
15.5	CARTOGRAPHIE NON INVASIVE ET MODELE INFORMATIQUE	87
16	REFERENCES.....	90

INTRODUCTION

1 INSUFFISANCE CARDIAQUE, ASYNCHRONISME ET RESYNCHRONISATION

La pandémie d'insuffisance cardiaque observée dans les pays occidentaux est un problème majeur de santé publique avec une prévalence d'environ 4% de la population adulte (10% pour les plus de 70 ans), responsable de près de 2% des dépenses de santé.¹ Le pronostic des patients insuffisants cardiaques reste sombre en dépit des progrès pharmacologiques dans le domaine avec une mortalité à 1 et 5 ans restant élevée. Environ 50% des patients insuffisants cardiaques présentent une altération de la fraction d'éjection ventriculaire gauche.² Cette altération de la fonction contractile est associée dans environ un tiers des cas de troubles de la conduction électrique. Différentes études ont permis de démontrer l'effet délétère propre de la séquence d'activation observée dans le cadre du bloc de branche gauche (BBG) justifiant d'une thérapeutique ciblée sur cette dysfonction électrique.^{3,4} L'interruption de la conduction dans la branche gauche engendre un asynchronisme d'activation et de contraction étagé entre oreillettes et ventricules, entre ventricule droit et ventricule gauche et entre les différentes parois du ventricule gauche. Les différents délais dans l'activation se traduisent par l'existence d'une répartition différentielle des conditions de charge segmentaire responsable à court terme d'une dégradation hémodynamique et à plus long terme d'un remodelage asymétrique électrophysiologique, moléculaire, cellulaire et tissulaire venant grever le pronostic de ces patients.⁵⁻⁸ Si le bénéfice hémodynamique apporté par la stimulation ventriculaire gauche a été mis en évidence dans le courant des années 1960, ce n'est qu'au début des années 1990 que la stimulation cardiaque a été pensée et appliquée comme une thérapeutique spécifique de l'asynchronisme cardiaque induite par le BBG.⁹⁻¹¹ En 1994, une équipe française a décrit l'amélioration hémodynamique aiguë puis clinique spectaculaire d'un patient insuffisant cardiaque en stade IV de la NYHA présentant un BBG complet associé à un bloc auriculo-ventriculaire du premier degré grâce à l'implantation d'un pacemaker quadruple chambre (biatrial et biventriculaire).¹¹ Le bénéfice procuré par une stimulation ventriculaire gauche plus ou moins associée une stimulation ventriculaire droite pour réaliser une stimulation biventriculaire (BIV) a ensuite été confirmé par une série d'études hémodynamiques aiguës invasives chez des patients en stade III-IV de la NYHA présentant un trouble de conduction intra-

ventriculaire.¹²⁻¹⁴ Une série de grands essais contrôlés, randomisés a permis d'établir le bénéfice clinique au long cours de la stimulation BIV sur de larges populations de patients insuffisants cardiaques à fraction d'éjection altérée, réfractaires au traitement médical (stade III-IV NYHA) avec trouble de la conduction intra-ventriculaire manifesté par un élargissement du QRS (≥ 120 , 130 ou 150 ms suivant les études).¹⁵⁻¹⁸ Ces essais ont démontré une amélioration de la classe NYHA, du score de qualité de vie, de la distance parcourue au test de marche de 6 minutes, du pic de $VO_{2\max}$ ainsi qu'une amélioration de la fraction d'éjection et une réduction des volumes ventriculaires gauches. Une réduction des hospitalisations a également été systématiquement observée. L'étude CARE-HF, étude centrale dans l'histoire de cette thérapeutique, a définitivement mis en évidence un gain significatif en terme de mortalité dans la population resynchronisée (RR:36%, $p < 0.002$ sur un suivi moyen de 24 mois par rapport au groupe de patients non implantés).¹⁹ Dès 2005, la société européenne de cardiologie recommandait la stimulation BIV chez les patients insuffisants cardiaques ($FE < 35\%$, NYHA III-IV) présentant un asynchronisme ventriculaire défini par une largeur du QRS ≥ 120 ms pour réduire les symptômes et les hospitalisations (classe I, niveau de preuve A) ainsi que la mortalité (classe I, niveau B – puis A en 2008).^{1,20}

Au début de cette thèse (année 2011), la principale limite de cette thérapeutique réside dans le nombre de patients non répondeurs. En effet, quelles que soient les études et le critère utilisé pour définir une réponse favorable, il existe une proportion importante de patients (entre 30 et 50 %) qui ne tirent pas bénéfice de cette thérapeutique.^{18,21} Une partie importante des efforts de recherche a porté sur l'évaluation de techniques d'imagerie permettant d'optimiser la sélection des candidats. En dépit de premiers résultats positifs, l'utilisation de l'échographie cardiaque pour mesurer la composante mécanique de l'asynchronisme ventriculaire a été freinée par la mise en évidence de problèmes majeurs de faisabilité et de reproductibilité.^{21,22} A ce jour aucun paramètre d'asynchronisme échographique n'est recommandé par les sociétés internationales pour la sélection des patients à la resynchronisation cardiaque et l'électrocardiogramme de surface reste l'outil de référence recommandé.¹ Les résultats d'analyse de sous-groupes des études REVERSE (QRS ≥ 120 ms) et MADIT-CRT (QRS ≥ 130 ms) réalisées chez des patients en classe I ou II de la NYHA, ont montré que seuls les patients ayant

une durée du QRS ≥ 150 ms tiraient bénéfice de la resynchronisation (critère clinique composite pour REVERSE, décès ou événements reliés à l'insuffisance cardiaque pour MADIT-CRT).^{23,24} De même, une méta-analyse ayant combiné les données de ces 2 essais et celles des études RAFT, COMPANION et CARE-HF a montré l'absence de bénéfice pour les patients avec une durée du QRS inférieure à 150 ms.²⁵ En parallèle à la durée du QRS, la morphologie du complexe QRS paraît prédominante dans le degré de réponse à la resynchronisation. Dans les études précédemment citées, seuls les patients présentant un bloc de branche gauche tiraient significativement bénéfice de la thérapie.^{26,27} Le prolongement de l'espace PR et la présence d'un bloc de branche droit ont été associés à un pronostic défavorable.²⁸

Les techniques de cartographie d'activation ventriculaire (endocardique comme épicaudique) se sont largement développées dans le domaine de l'électrophysiologie ablatrice mais sont restées anecdotiques et du domaine de la recherche dans le cadre de la resynchronisation en raison de leur caractère invasif et chronophage. Elles permettent toutefois une analyse précise et détaillée de la séquence d'activation ventriculaire, élément clé de la compréhension des mécanismes impliqués dans cette thérapeutique. Les techniques de cartographie électrique non invasives basées sur la résolution mathématique du problème inverse paraissent extrêmement prometteuses pour répondre aux limites de l'électrocardiogramme de surface (approche grossière de la séquence d'activation) et des techniques invasives (acquisition non invasive en un seul battement de la séquence d'activation ventriculaire tridimensionnelle reconstruite à partir de centaines d'électrogrammes en opposition à un recueil fastidieux cycle à cycle des électrogrammes locaux).^{29,30}

2 OBJECTIFS DE CE TRAVAIL

La thérapie de resynchronisation est un traitement validé et efficace sur la réduction de morbi-mortalité des patients insuffisants cardiaques présentant une durée du QRS ≥ 120 ms. Contrairement aux autres traitements de l'insuffisance cardiaque, les résultats cliniques ont précédé les travaux de recherche expérimentale, si bien que les mécanismes à l'œuvre dans le processus de resynchronisation cardiaque sont imparfaitement connus. En dépit d'une

littérature relative à l'asynchronisme (mécanique principalement) très abondante, l'ECG de surface reste l'unique médium recommandé pour l'évaluation de l'asynchronisme des patients candidat à la resynchronisation cardiaque. Le taux de non réponse à la thérapie ne s'en trouve pas réduit.

Le travail présenté ici a débuté en 2011 et a été réalisé en collaboration entre les laboratoires des professeurs Haïssaguerre à Bordeaux et Prinzen à Maastricht où j'ai passé un an (année 2012). Il comprend des expérimentations chez l'homme (service d'électrophysiologie de Bordeaux) et chez l'animal (laboratoire de physiologie de Maastricht) ainsi que des données provenant d'un modèle informatique d'insuffisance cardiaque développé par l'équipe du professeur Arts à Maastricht. L'objectif de ce travail était de façon générale de mieux appréhender les mécanismes impliqués dans les réussites et les échecs associés à la resynchronisation BIV en insistant sur la caractérisation du substrat électrique éligible à la thérapie et l'intérêt de la resynchronisation électrique pour la réponse.

Nous avons successivement tentés de répondre aux questions suivantes :

1. Y a-t-il une relation entre l'asynchronisme électrique intrinsèque défini par la durée du QRS et la réponse hémodynamique à la resynchronisation BIV ?
2. Une approche plus détaillée de la séquence d'activation et de l'asynchronisme ventriculaire par cartographie électrocardiographique (ECM) est-elle supérieure à l'analyse de l'ECG 12 dérivations pour la sélection des candidats à la resynchronisation ?
3. Y a-t-il un effet différentiel de la stimulation BIV en fonction du substrat ? Pourquoi les patients avec BBG sont-ils a priori de bons candidats à la resynchronisation cardiaque ? Existe-t-il un sous-groupe de patients avec QRS fin ou avec bloc indifférencié répondant favorablement à la resynchronisation ?
4. Existe-t-il des différences entre la séquence d'activation ventriculaire induite par stimulation apicale ventriculaire droite et le BBG pouvant expliquer des différences de réponse après resynchronisation ?
5. Quels sont les mécanismes permettant d'expliquer un bénéfice comparable entre stimulation mono-VG et stimulation BIV ?

6. Quel est l'intérêt de la stimulation multipoints VG par rapport à la stimulation BIV traditionnelle ?

Les différents travaux présentés ici ont donné lieu à 8 publications dans des journaux internationaux à comité de lecture. L'essentiel de ce manuscrit réside dans la présentation de ces articles et la discussion des résultats observés.

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Cardiac Resynchronization Therapy – Refocus on the Electrical Substrate –

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Cardiac resynchronization therapy (CRT) is an established treatment for selected heart failure patients with conduction disease. Many studies aimed at quantifying mechanical dyssynchrony in CRT candidates when it became apparent that 30–50% of CRT recipients showed no improvement after implantation. As these, often echocardiography-based, measurements have not yet succeeded in estimating the mechanical substrate in an accurate and reproducible manner, interest in electrical substrate has renewed. In this review, current knowledge concerning electrical substrate in CRT candidates will be explored and applied to current CRT practice, highlighting why the electrical substrate is both essential and sufficient for successful CRT. Finally, novel ways to better measure and treat the electrical substrate are discussed. (*Circ J* 2011; **75**: 1297–1304)

Key Words: Cardiac resynchronization therapy; Electrophysiology; Left bundle branch block

As its name suggests, cardiac resynchronization therapy (CRT) aims to treat the electrical substrate in symptomatic heart failure (HF) patients with reduced LV ejection fraction (EF) and wide QRS complex. A recent meta-analysis pooled more than 3,000 CRT patients from 6 trials and reported a reduction in all-cause mortality of 29% and a reduction in the number of new hospitalizations for worsening HF of 37%.¹ Nevertheless, a QRS duration >120ms has proven to be a moderate predictor of CRT efficacy, as 30–50% of implanted patients do not respond to the therapy. This has sparked major efforts into identifying patients who benefit from CRT by investigating mechanical dyssynchrony. However, the relatively slow improvement in CRT efficacy in recent years has renewed interest in the electrical substrate. It has become increasingly clear that left bundle branch block (LBBB) is the hallmark conduction disease that is treatable by CRT, as evidenced by efficacy of CRT in canine hearts with isolated LBBB and in CRT patients with LBBB compared to CRT patients with other conduction disorders.^{2,3}

In this review we will explore current knowledge concerning the electrical substrate in CRT candidates and apply this to current CRT practice. We will then discuss why the electrical substrate is both essential and sufficient for successful CRT. We will show that this is true if the electrical substrate is defined more accurately than just by duration of the QRS complex.

LBBB

A century has passed since Eppinger and Tothberger first described LBBB by associating distinctive electrophysiological changes with the destruction of only a small region in the interventricular septum in the canine heart.⁴ The typical QRS-morphology changes seen in the esophageal-to-rectal lead in the dogs were directly extrapolated to leads II and III in human patients. This misinterpretation caused LBBB to be erroneously diagnosed as right bundle branch block (RBBB) and vice versa in the first quarter of the past century.

It was only until decades after the rectification that the anatomy of the left bundle branch (LBB) and the significance of its dysfunction were investigated in detail. In 1972, Demoulin et al reported their histopathological findings in human patients without known cardiac disease, showing that the LBB emerges from the His bundle between the non-coronary and right-coronary aortic cusps and runs as a 6–10-mm wide ribbon-like structure inferiorly and slightly anteriorly over the septal subendocardium.⁵ With considerable variation, the fibers of the LBB quickly separate to form fasciculi in anterior, posterior and often septal main radiations (**Figure 1**). The LBB enables fast activation of the left ventricle (LV) because it ends in a rich peripheral Purkinje network that couples with individual (sub)endocardial myocardial cells.⁶ Extensive electrical mapping in isolated human hearts with an intact LBB showed up to 3 LV endocardial breakthrough sites that resulted in a rapid electrical activation of the LV.⁷

In 1984 Vassallo et al reported their results of an endo-

Received April 4, 2011; accepted April 6, 2011; released online April 29, 2011

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ISSN-1346-9843 doi:10.1253/circj.CJ-11-0356

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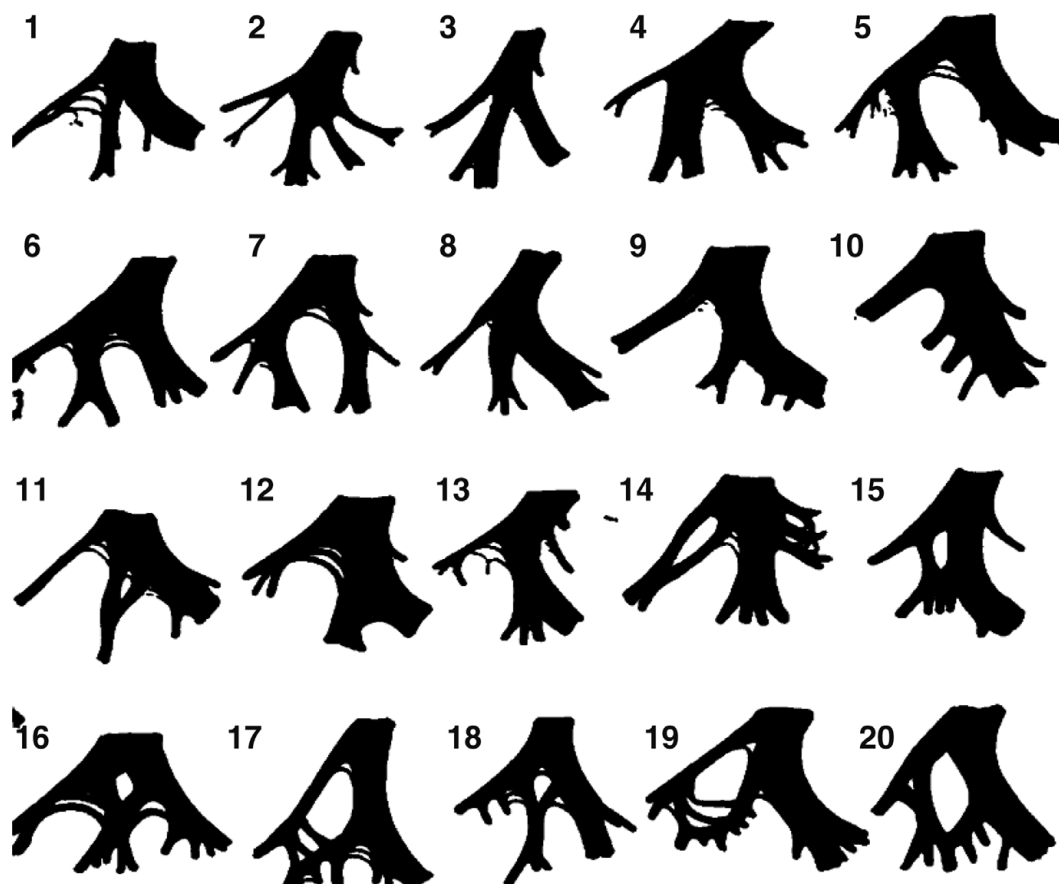


Figure 1. Diagrammatic sketches of the left-sided conduction system as observed in 20 normal hearts (reproduced with permission from BMJ Publishing Group⁵).

cardial catheter mapping study in 18 patients with LBBB and concluded that LV endocardial activation in LBBB occurred as a result of right-to-left transseptal activation and that the LV endocardial activation sequence in these patients was heterogeneous.⁸ The heterogeneous activation patterns could be the result of (1) the varying anatomy of the LBB as shown in **Figure 1**, (2) variability in the location of LBB disease, being either proximal or distal or (3) the fact that cellular uncoupling as a consequence of LV hypertrophy can give rise to a LBBB-like QRS complex. Surprisingly, there is very little information about the nature of LBBB or about the eliciting factors (other than myocardial infarction). It is debated whether LBBB is the cause or consequence of HF. In favor of the first idea are findings from experiments in canine hearts where proximal ablation of the LBB was performed.⁹ In those experiments LBBB alone lead to a reduction in the EF, LV dilatation and hypertrophy.² On the other hand, in the case of cellular uncoupling the LBBB-like conduction pattern is the consequence of cardiac dysfunction.

Recently, a combination of contact and non-contact mapping studies have shown that in LBBB patients with HF the activation wavefront originating from the right ventricle (RV) caused LV endocardial breakthrough in different septal regions.^{10,11} In some patients, endocardial LV breakthrough occurred in the vicinity of the conduction system in the mid-septal region, which could suggest activation by slow con-

duction through the LBB and not via right-to-left transseptal activation.¹⁰ Narula reported in 1977 that he could abolish the electrocardiographic signs of LBBB in 25 patients by distal His-bundle pacing in the RV, indicating that the lesion in these LBBB patients was very proximal in the rapid conduction system (just below the atrioventricular (AV) node).¹² The aforementioned mapping and pacing studies suggest that, at least in some patients the disruption of LBB conduction is proximal. Endocardial non-contact mapping also identified that in approximately two-thirds of the patients with HF and LBBB, the electrical wavefront propagates over the LV apex in a “U-shaped” manner around anterior and posterior lines of block.¹¹ The existence of these lines of conduction block was also shown by electrocardiography imaging, a non-invasive epicardial mapping tool.¹³ Since LV pacing modifies the position of the lines of block, these lines appear to be functional and not fixed to anatomical structures or areas of ischemia.¹¹

In canine hearts creation of proximal LBBB leads to doubling of the QRS duration and electrical mapping shows that the onset of electrical activation is located in the RV (**Figure 2**). The electrical wavefront then slowly propagates towards the lateral wall of the LV. Preliminary non-contact mapping data also reveal lines of functional block, similar to those in many LBBB patients (**Figure 3**). In these otherwise healthy LBBB hearts the observed lines of block are modified

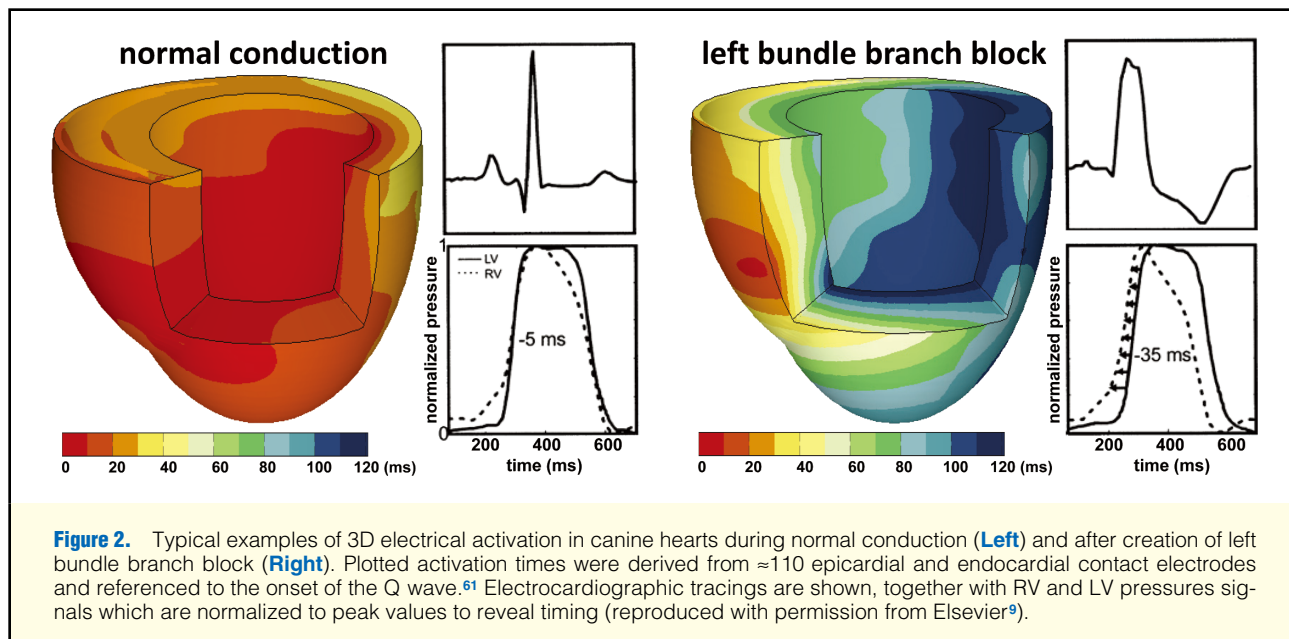


Figure 2. Typical examples of 3D electrical activation in canine hearts during normal conduction (Left) and after creation of left bundle branch block (Right). Plotted activation times were derived from ≈ 110 epicardial and endocardial contact electrodes and referenced to the onset of the Q wave.⁶¹ Electrocardiographic tracings are shown, together with RV and LV pressures signals which are normalized to peak values to reveal timing (reproduced with permission from Elsevier⁹).

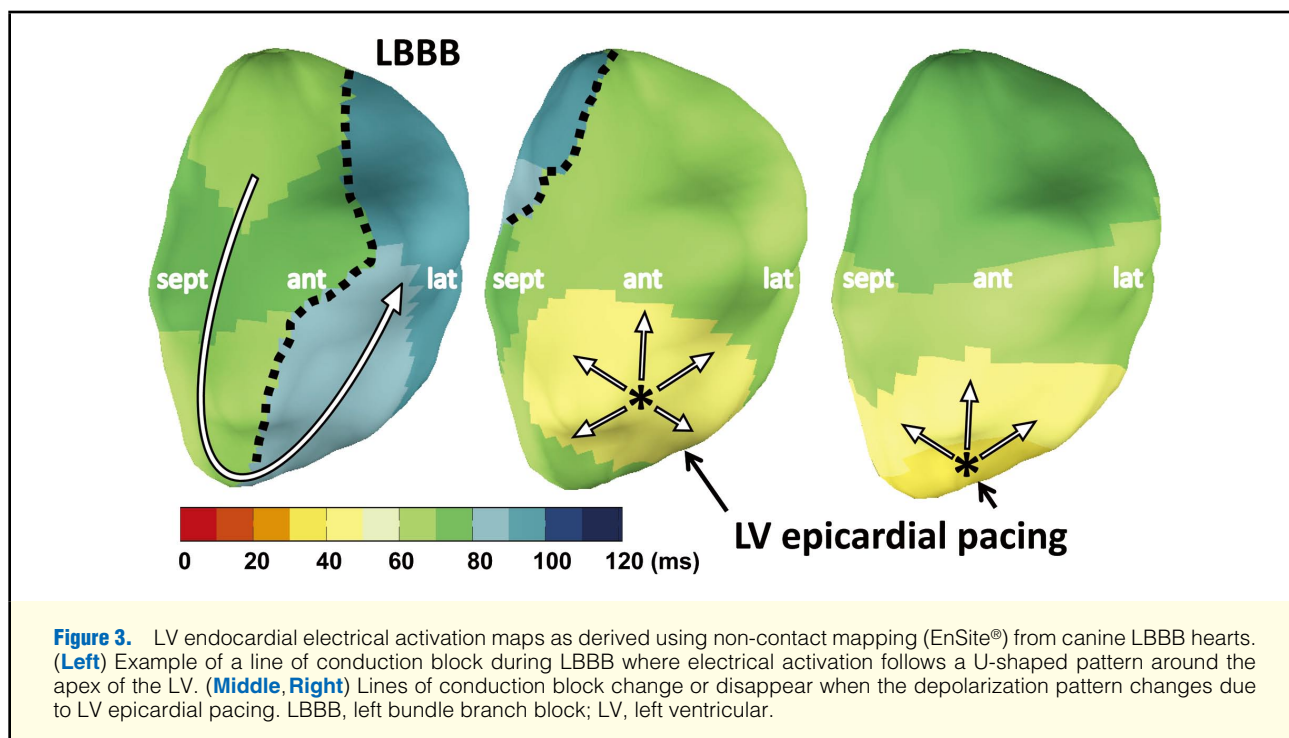


Figure 3. LV endocardial electrical activation maps as derived using non-contact mapping (EnSite[®]) from canine LBBB hearts. (Left) Example of a line of conduction block during LBBB where electrical activation follows a U-shaped pattern around the apex of the LV. (Middle, Right) Lines of conduction block change or disappear when the depolarization pattern changes due to LV epicardial pacing. LBBB, left bundle branch block; LV, left ventricular.

by LV pacing at different sites. Combining the observations in the canine model with the aforementioned patient studies suggests that at least a sizeable number of CRT candidates with LBBB have a proximal lesion.

Even though in most CRT trials, patients were required to have QRS duration of at least 120 ms, approximately one-third of these patients did not have LBBB.^{3,14} On top of that, one-third of patients diagnosed with LBBB by conventional electrocardiographic criteria may not have true complete LBBB, but likely have a combination of LV hypertrophy and left anterior fascicular block.^{8,15} Specific ECG criteria are required for LBBB (in addition to QRS width ≥ 120 ms)

such as a broad notched or slurred R wave in leads I, aVL, V₅ and V₆, an occasional RS pattern in V₅ and V₆ attributed to displaced transition of QRS complex, and absent Q waves in leads I, V₅, and V₆ (in the absence of a large anterior-apical infarction).¹⁶ When these criteria are not met it is likely that patients have RBBB or conduction slowed by LV hypertrophy.

Recent Focus on the Mechanical Substrate

Asynchronous activation leads to abnormal contraction, and advanced measurements (MRI tagging) in asynchronous

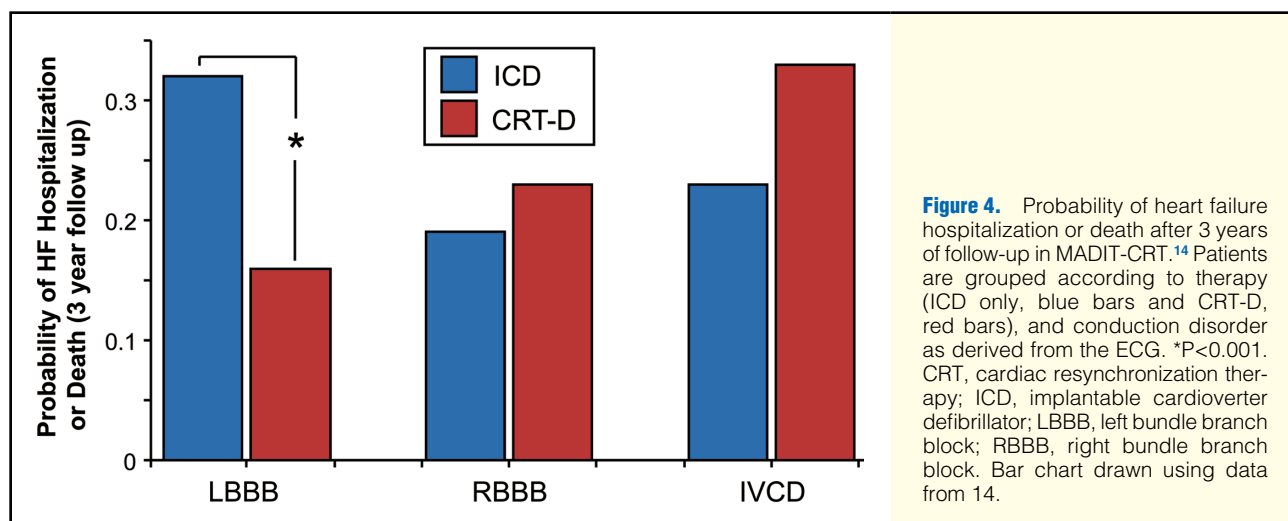


Figure 4. Probability of heart failure hospitalization or death after 3 years of follow-up in MADIT-CRT.¹⁴ Patients are grouped according to therapy (ICD only, blue bars and CRT-D, red bars), and conduction disorder as derived from the ECG. * $P < 0.001$. CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; RBBB, right bundle branch block. Bar chart drawn using data from 14.

ventricles showed that timing differences in shortening are larger than in electrical activation.¹⁷ The “exaggeration” of asynchrony by mechanical measurements appeared to make mechanical measurements a useful additional tool for selection of CRT candidates, also because mechanical dyssynchrony appears to relate to EF in patients with RV pacemakers.¹⁸ This idea resulted in a search for methods to measure mechanical dyssynchrony, which could better predict responders than solely QRS duration. Since echocardiography is non-invasive and relatively affordable, multiple echocardiography-based mechanical indices were proposed. Unfortunately, dyssynchrony measurements have yet failed to show predictive value for CRT response in prospective trials. In the multicenter PROSPECT (Predictors of Response to CRT) trial multiple echocardiography dyssynchrony parameters were tested, with disappointing results in their ability to predict CRT response.¹⁹ Both for a positive clinical or volume response to CRT, the measurements resulted in an area under the receiver-operating characteristics (ROC) curve of at most 0.62. A more recent multicenter trial performed in Japan confirmed that echocardiographic parameters did not show significant power to detect CRT responders independently with comparable ROC curves.²⁰ While the aforementioned studies primarily used tissue Doppler imaging, a more recent study, using speckle-tracking techniques indicated that the thus assessed radial strain dyssynchrony increases the ROC for volume response to 0.79.²¹ However, another speckle-tracking study provided evidence that the amount of septal positive strain (stretch) during systole following a short period of early systolic shortening (septal rebound stretch) shows a ROC for volume response of 0.89. Being a stretch-derived measurement, septum rebound stretch reflects “dyscoordination” rather than “dyssynchrony”.²² Whether this or other dyscoordination indices are useful in common practice has yet to be proven in multiple centers.

The other attempted application of mechanical dyssynchrony for predicting CRT response was in patients with narrow QRS width. Some HF patients with narrow or only slightly prolonged QRS duration (<130ms) were shown to have mechanical dyssynchrony as derived from tissue Doppler imaging and comparable techniques.^{23–25} Small, single-center studies reported CRT benefits in patients with mechanical dyssynchrony and narrow QRS complex.^{23–25} However, these findings were not corroborated by the RethinQ (Cardiac

Resynchronization Therapy in Patients with Heart Failure and Narrow QRS) trial where 172 patients were randomized to receive ICD-CRT implantation with CRT switched “OFF” or “ON”.²⁶ After 6 months, the ICD-CRT group and the ICD-only group did not differ in peak oxygen consumption, HF event rates or LV dimensions as measured by echocardiography. So far no attempts to use indices of mechanical dyscoordination in this patient category are known.

Electrical Substrate Is Essential for Effective CRT

While diagnosis of the mechanical substrate for CRT is suffering some problems, recent studies shed new light on the relevance and usefulness of improved measures of the electrical substrate for CRT. A recent electrical mapping study showed that “true LBBB” was only seen in patients with a QRS duration >140ms.²⁷ Indeed, patients with QRS duration >150ms and LBBB morphology showed the highest response rates in large multicenter trials. The REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study failed to show a significant difference in their primary endpoint (percentage worsening in the HF clinical composite response score), except for patients with QRS duration >152ms ($n=307$), where there was a clear difference (odds ratio (OR) 0.42, confidence interval (CI) 0.22–0.81).²⁸ In the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial, CRT-D resulted in a 52% decrease in risk of death or HF in the subgroup of patients with QRS duration ≥ 150 ms ($n=1,175$) as compared to ICD only patients.^{29,30} This astonishing result is the reason the trial met its primary endpoint for all CRT-D patients, despite the subgroup of 645 patients with QRS duration <150ms that did not show a reduction. Similarly, a recent MADIT-CRT subanalysis investigated patients with LBBB at baseline ($n=1,281$) and found a decrease of 53% in the aforementioned endpoints in patients with CRT-D (Figure 4). These data, in combination with a trend to worsening in the subgroups of patients with RBBB and IVCD, stress the importance of LBBB as electrical substrate.¹⁴ In addition, the risk of ventricular tachycardia, ventricular fibrillation, or death was decreased significantly in CRT-D patients with LBBB but not in non-LBBB patients. In accordance, RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) reported reductions in mortality or

hospitalization for HF only for the subgroup of patients who had QRS duration >150 ms or LBBB.³¹ A recent retrospective analysis of the Medicare Implantable Cardioverter-Defibrillator Registry (2005–2006) showed that almost one-third of the $\approx 15,000$ CRT-D patients had RBBB or intraventricular conduction delay, rather than LBBB.³ After 3 years, 40.3% of patients with RBBB and 34.2% of patients with intraventricular conduction delay had died, as opposed to 29.7% of patients with LBBB.

If LBBB indeed predicts CRT response, it is likely that the 12-lead ECG holds additional valuable biomarkers but research into alternative measurements has been scarce. Sweeney et al carefully inspected standard 12-lead ECGs of 202 LBBB patients indicated for CRT.³² Based on their comparisons of baseline and post-implant ECGs, the authors introduced new measurements that predicted CRT response (defined as at least 10% reduction in end-systolic volume as derived by echocardiography at 6 months). A notch, which occurred after 40 ms of QRS onset, was regarded as the transition from RV to LV depolarization and the time difference between this notch and the end of QRS was indicated as the LV activation time (LVAT_{max}). QRS duration was weakly associated with reverse remodeling probability and this relationship was replaced by LVAT_{max} in the multivariable model. A longer LVAT_{max} at baseline was predictive of CRT response (OR 1.30 for each 10 ms increase up to 125, $P=0.001$). The Selvester QRS score was used to quantify LV scar and a higher score was detrimental to volumetric response (OR 0.49 for each 1-point increase from 0 to 4, $P=0.002$).²⁷ The appearance of anterior forces in the precordial leads after implantation (change in R amplitude in V₁ and V₂ in the expected direction) was also predictive of CRT response. An alternative method to non-invasively estimate LV electrical asynchrony is by calculating the delay between QRS onset and LV lead depolarization. Varma found in HF patients that this delay exceeded 100 ms in 87% of LBBB patients as compared to 45% of RBBB patients, even though there was no difference in QRS duration.³³ Singh et al showed that CRT patients with a reduced LV lead electrical delay ($<50\%$ of the QRS duration) before biventricular (BiV) pacing had a worse clinical outcome at 12 months.³⁴

Studies investigating ECG beyond the surface ECG or pacemaker lead electrograms are even more scarce, because evaluation of the cardiac electrical activation sequence by catheter mapping in CRT candidates is time-consuming, cumbersome, and not without risk. As discussed earlier, lines of conduction block are seen in most LBBB patients, as shown by endocardial and epicardial non-contact mapping studies.^{11,13} The implications of these lines of block have been investigated in a small observational study where non-contact mapping was performed in 23 CRT candidates; 12 of the 18 patients who had lines of conduction block before implantation were volumetric CRT responders at 3 months as opposed to 1 of the 8 patients who had homogeneous endocardial conduction ($P=0.01$).³⁵ This study confirmed that the benefit of CRT is more dependent on specific LV activation patterns rather than on total LV activation time, which could explain why LVAT_{max} beyond 125 ms, and in some studies QRS duration, are poor individual predictors of response.^{32,36}

Electrical Substrate Is Sufficient for Effective CRT

The aforementioned findings give rise to the notion that an “adequate amount” of conduction delay needs to be present for CRT to be efficient. Whether additional factors such as

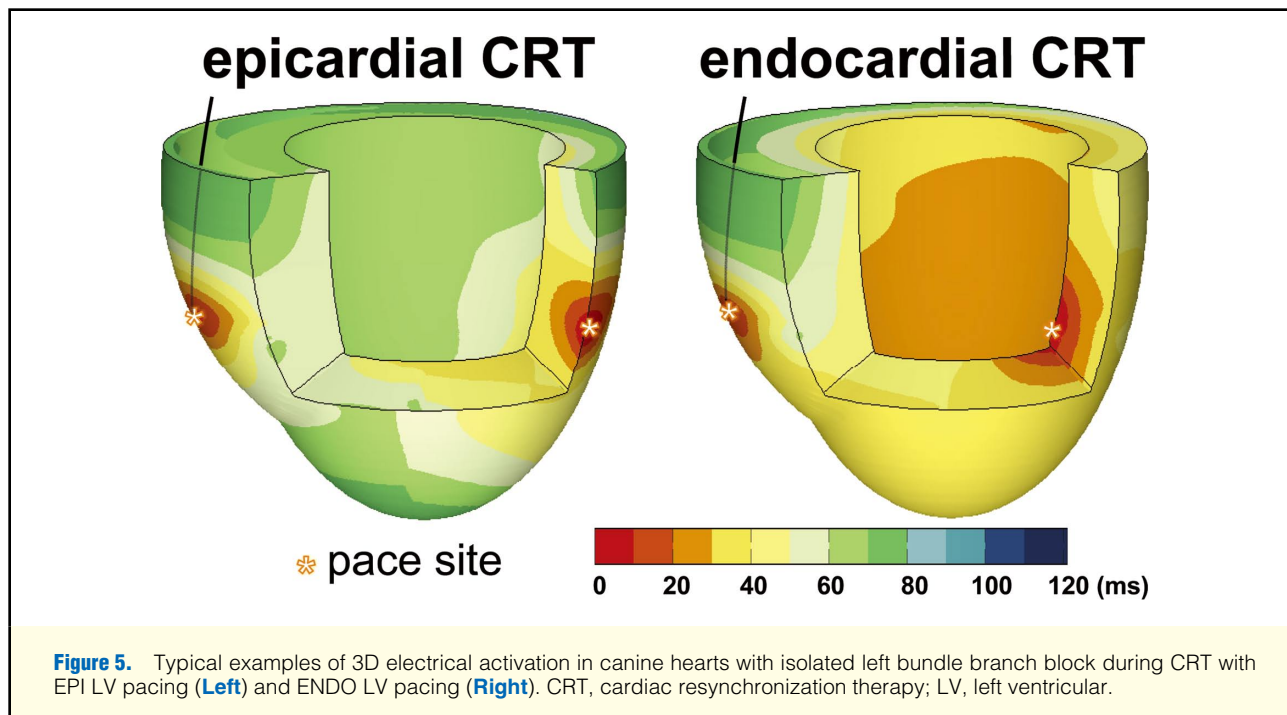
LV systolic dysfunction need to coexist with electrical asynchrony for CRT to be successful, is important for understanding the therapy and better selection of CRT candidates. In healthy canine hearts, isolated LBBB induces electrical and mechanical asynchrony that in its turn causes loss of LV pump function and ventricular remodeling.³⁷ In these hearts, isolated CRT largely reversed global and regional function and structural abnormalities, indicating that LBBB as electrical substrate is sufficient for acute and long-term responses to CRT.² Recently, multiple clinical trials have tested this idea by investigating CRT efficacy in HF patients who were not severely symptomatic (NYHA classes I and II).

The MIRACLE ICD II (Multicenter InSync Randomized Clinical Evaluation II) trial showed that CRT for 6 months lead to improvement in cardiac structure and function, together with improvement in NYHA class and clinical composite response score.³⁸ Reductions in LV dimensions were also seen in the mildly symptomatic HF subgroup (NYHA classes I and II) of the CONTAK-CD (CONTAK-Cardiac Defibrillator) trial.³⁹ Initial results of the REVERSE trial were disappointing as the difference in the percentage of NYHA I–II patients who worsened in clinical composite score after 12 months among the ICD-CRT patients vs. ICD-only patients failed to reach significance (16% vs. 21%, $P=0.10$).²⁸ However, after a follow-up of 24 months in a subgroup of European patients, the difference did become significant, with worsening in 19% of CRT patients vs. 34% in control patients ($P=0.01$).⁴⁰ For both follow-up periods, CRT resulted in a reduction in HF hospitalization and greater improvements in cardiac structure and function. In the MADIT-CRT trial, a 41% reduction in HF events during an average follow-up of 2.4 years was seen in favor of the CRT-ICD patients.^{30,41} Finally, RAFT followed 1,438 NYHA II patients for an average of 40 months and found a 29% reduction in all-cause mortality and a 30% reduction in hospitalization for HF.³¹

Given the electrical similarity of the spontaneously occurring and the RV pacing-induced LBBB, several centers have explored the feasibility of “upgrading” patients without HF with already implanted RV pacemakers to BiV ones or, in the case of a new implant, to use BiV pacing from the beginning in select patients. Although large, prospective, randomized controlled studies are currently lacking, there are several retrospective observational series or small prospective trials demonstrating a clinical benefit of upgrading to BiV pacing, regardless of QRS duration and even in patients with normal LVEF.^{42–45} The mentioned clinical studies confirm the findings from animal research and remind us that the underlying electrical substrate can be treated, also in the absence of HF symptoms, thus preventing or delaying the development of HF. These insights have lead the ESC guidelines to recently extend recommendations for CRT implantation to patients with LVEF $<35\%$ with NYHA class II and QRS ≥ 150 ms (class I recommendation) or narrow QRS and regular pacemaker indication (class IIb recommendation).⁴⁶

The Role of the Site of Pacing

From a theoretical point of view, the sites of pacing that may be considered optimal are those that establish the greatest reduction in total activation time. CRT is most often performed by pacing the RV (commonly at the apex) and the LV in a simultaneous or sequential order. The generation of 2 activation wavefronts is not physiological but is considerably better than the activation during LBBB.⁹ Commonly, the LV lead is placed in the latest activated region, which in LBBB



is usually the basal part of the posterolateral wall.^{10,11} By using extensive epicardial mapping and magnetic resonance imaging strain analysis, Helm et al demonstrated that in canine LBBB hearts the exact LV site of pacing is not very critical, as a good (>70% of maximum) increase in LV dp/dt_{max} was achieved by pacing in 43% of the LV wall.⁴⁷ The latter region included the LV apex, which was also shown to provide excellent effects in other studies in canine hearts.^{9,48,49} In contrast to these findings, a recent publication about the MADIT-CRT study showed that LV apical pacing provided an inferior effect.⁵⁰ A potential explanation for these contradictory findings may be that LV apex pacing requires a shorter AV delay to be optimal in canine hearts.⁹ Indeed, in CRT patients the increase in LV dp/dt_{max} during LV apex pacing is low when using an average AV delay, but almost maximal when using the optimal AV delay.⁵¹

Most studies show that the amount of non-responders is highest in patients who suffer from ischemic cardiomyopathy (ICM). One possible mechanism is that there is insufficient viable tissue to allow an increase in contractility by CRT. Another possible mechanism lies in modification of the electrical substrate. According to this idea, the extent of resynchronization would be limited as a result of slow-conducting or non-conducting regions. This would mean that a good response to CRT in ICM patients not only requires clear conduction disease, but also the capability to properly resynchronize the heart. An important feature in this regard is the site of pacing, as pacing in the vicinity of scar tissue can compromise conduction. In canine hearts with LBBB and transmural infarction, pacing away from the infarcted regions resulted in a similar CRT response as in non-infarcted canine LBBB hearts.⁴⁸

During the routine coronary sinus approach, the LV is paced at the epicardial surface. However, under physiological conditions, excitation of the LV initiates at the endocardium.⁷ In canine LBBB hearts, endocardial LV pacing during CRT consistently improved systolic LV pump function, reduced

electrical dyssynchrony and decreased dispersion of repolarization, as compared to epicardial LV pacing at the same site (**Figure 5**).⁴⁹ Additionally, the hemodynamic effects for endocardial sites were less dependent on location and AV delay than epicardial sites. More information is becoming available about the acute hemodynamic effects of LV endocardial pacing in CRT candidates. Spragg et al investigated 7 ICM patients and CRT systems where LV endocardial and epicardial pacing at immediately transmural sites gave equivalent LV dp/dt_{max} values.⁵² However, LV dp/dt_{max} at best LV endocardial sites was greater than conventional CRT. Similarly, Derval et al investigated up to 11 LV pacing sites (10 endocardial sites and 1 epicardial coronary sinus site) in 35 non-ischemic dilated cardiomyopathy (DCM) patients.⁵³ When comparing the effect of pacing the endocardium with that of the immediately opposite coronary sinus electrode, no statistically significant increase in LV dp/dt_{max} was observed, although LV dp/dt_{max} tended to be higher during endocardial CRT. However, single-site LV pacing at the optimal endocardial site doubled LV dp/dt_{max} as compared to conventional CRT. The superior effect of the optimal endocardial site over conventional CRT on contractility was recently confirmed by Ginks et al, who investigated LV endocardial CRT in 15 CRT candidates.⁵⁴ In agreement with the earlier studies, the optimal endocardial pacing site was heterogeneous between patients. Given individual variations in etiology, severity, patterns of delayed ventricular activation, location of regions of scarring, and extent of mitral regurgitation in HF, it indeed seems unlikely that 1 pacing site will “fit all”. Individual tailoring of endocardial CRT by searching for the optimal pacing site within the endocardium is warranted.

LV endocardial pacing in humans can be established through an atrial transseptal approach, which is shown to be technically feasible and effective during acute and mid-term follow-up.^{55–57} Alternatively, a left transapical approach can be used.⁵⁸ The ultimate method to pace the LV endocardium would require (1) flexibility in placing the electrode, as the

optimal site may differ between patients, and (2) absence of a pacing lead in the LV cavity to minimize risk of thromboembolic events. One approach would be leadless pacing, by implanting an electrode at the desired endocardial location followed by retraction of the lead and stimulation of the implanted electrode through ultrasound⁵⁹ or magnetic stimulation.⁶⁰

Conclusions

For optimal CRT effect, it is imperative that the correct electrical substrate exists, preferably in the form of true LBBB, and that it is treated as such. It would not be surprising to see future guidelines extend their inclusion from only including patients with severe symptomatic HF to patients with specific electrical substrate. With the aid of endocardial LV pacing, with or without RV pacing, patient-specific tailoring of CRT can boost its efficacy to new levels. Finally, better understanding of the various forms of LBBB and its etiology will be of great importance for better application of CRT in the future.

Acknowledgments

Research of Marc Strik and Frits W. Prinzen was supported by a grant from the Center for Translational and Molecular Medicine (CTMM) in The Netherlands. Sylvain Ploux is the recipient of a research grant from the French Federation of Cardiology.

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MATERIELS & METHODES

4 RECONSTRUCTION NON INVASIVE DE L'ACTIVITE ELECTRIQUE CARDIAQUE

4.1 L'ELECTROCARDIOGRAMME 12 DERIVATIONS DE SURFACE

Un électrocardiogramme de surface est généré à partir du recueil à la surface du corps des modifications cycliques du champ électrique induites par les séquences d'activation se propageant au sein du myocarde. Willem Einthoven est considéré comme le père de l'électrocardiographie moderne avec la mise au point du galvanomètre à corde capable d'enregistrer les potentiels de surface à l'aide de dérivations bipolaires :

-DI entre bras gauche et bras droit

-DII entre pied gauche et bras droit

-DIII entre pied gauche et bras gauche

En 1938, un set de six d'électrodes précordiales unipolaires destinées à explorer l'activité cardiaque dans le plan horizontal est additionné aux 6 électrodes bipolaires. Ces électrodes sont référencées au terminal central de Wilson qui constitue une électrode neutre.

Sur le même principe les électrodes unipolaires ont été développées (Goldenberg 1942):

-aVR= $BD - \frac{1}{2}(BG+PG)$

-aVL= $BG - \frac{1}{2}(BD+PG)$

-aVF= $PG - \frac{1}{2}(BD+BG)$

L'électrocardiogramme 12 dérivations permet ainsi une approche de première intention de l'activité électrique cardiaque et est utilisé en pratique quotidienne à très large échelle avec une utilité indiscutable dans de nombreuses situations cliniques. Cette technique a très peu évolué au cours du dernier demi-siècle et il existe un degré de résolution spatiale limité ne permettant pas une approche précise et détaillée des séquences d'activation auriculaire et ventriculaire, préalable indispensable à une bonne compréhension des mécanismes impliqués dans différentes pathologies : arythmies auriculaire ou ventriculaire, QRS large et effet de la resynchronisation biventriculaire ...

4.2 CARTOGRAPHIE DE POTENTIELS DE SURFACE, BSPM

Pour répondre aux limites de l'électrocardiogramme de surface, une technique d'imagerie de l'activation électrique basée sur les potentiels de surface (body surface potential maps, BSPM) a été développée. Grâce à l'emploi de nombreuses électrodes (jusqu'à plusieurs centaines) distribuées tout autour du thorax, les BSPM permettent le recueil de potentiels de surface thoracique unipolaires et une visualisation tridimensionnelle des potentiels de surface dans le temps (une des électrodes éloignée sert d'électrode de référence). Cette technique qui n'est pas de pratique courante a démontré sa supériorité par rapport à l'ECG standard pour la détection de zones de nécrose (en particulier VG postérieure, ou ventriculaire droite), ou la détection d'une ischémie myocardique à l'épreuve d'effort.³¹ Néanmoins la résolution spatiale reste non optimale, limitée par de 2 problèmes physiques 1/ l'activité en un point de surface résulte en partie de l'activité électrique globale du cœur, 2/ les signaux de surface subissent une atténuation due au volume thoracique. Il est ainsi difficile de discerner deux activités électriques concomitantes avec cette technique (stimulation BIV par exemple).

En réponse à ces limitations, des techniques de reconstruction du signal cardiaque épicardique par résolution mathématique du problème inverse ont été développées permettant une représentation de l'activité électrique cardiaque de très grande précision (imagerie électrocardiographique ou cartographie d'activation électrocardiographique non invasive).

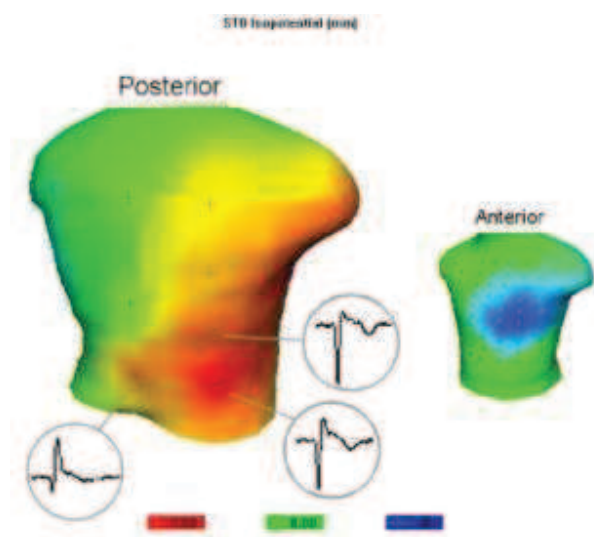


Figure 1 : Exemple de BSM avec projection thoracique tridimensionnelle

4.3 IMAGERIE ELECTROCARDIOGRAPHIQUE, OU CARTOGRAPHIE D'ACTIVATION

ELECTROCARDIOGRAPHIQUE NON INVASIVE- ELECTROCARDIOGRAPHIC

MAPPING ECM.

Une partie importante des travaux réalisés dans ce travail s'appuie sur la réalisation et l'interprétation de cartes non invasives réalisées dans différentes conditions d'activation (rythme spontané versus rythme stimulé). Le système de cartographie électrocardiographique utilisé (Electrocardiographic mapping ECM, de Cardio Insight technologies, Cleveland US) est une technique de cartographie électrique haute densité non invasive de l'activation épicardique. Le système acquiert des électrogrammes de surface à partir d'une veste dédiée équipée de 250 électrodes de contact. La position des électrodes par rapport à la géométrie cardiaque est localisée grâce à la réalisation d'un scanner thoracique. Les données électriques et anatomiques ainsi combinées sont utilisées pour la résolution mathématique du problème inverse visant à identifier les potentiels et électrogrammes à l'origine des signaux enregistrés en surface (figure 2).³²

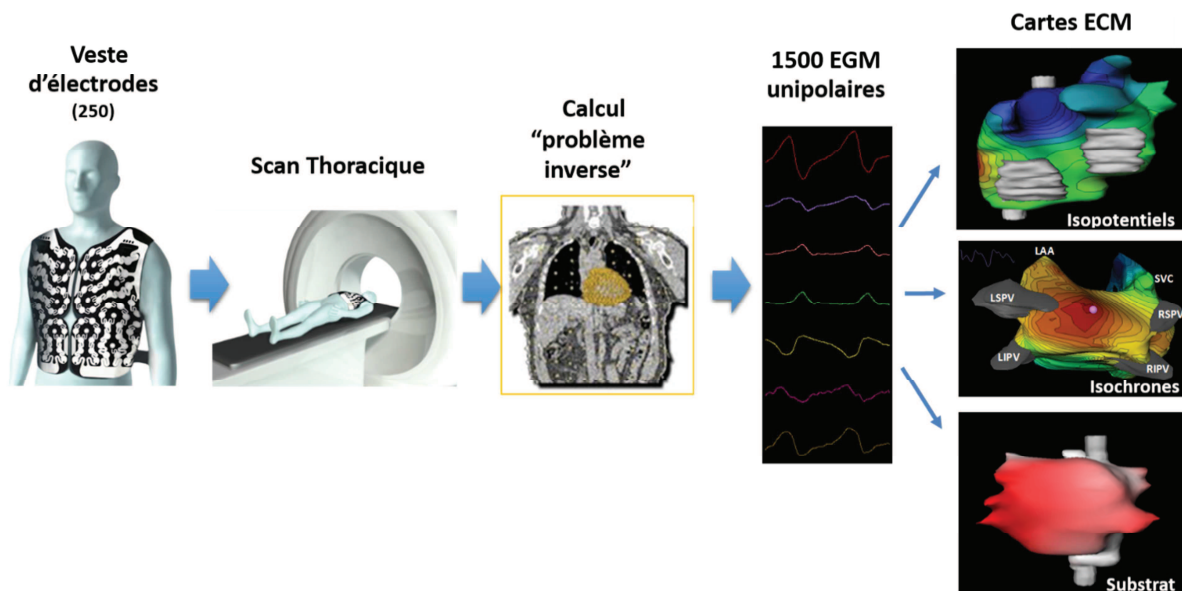


Figure 2 : Principe de réalisation de cartes ECM

Hardware

La veste est un gilet supportant 250 électrodes de contact pré-gélifiées réparties sur tout le thorax. Comme pour le BSM, les électrodes recueillent des potentiels de surface thoracique unipolaires (une des électrodes éloignée du cœur sert d'électrode de référence). Cette veste ajustable existe en différentes tailles, est à usage unique et ne doit pas être repositionnée sur le patient une fois en place. Le patient, porteur de la veste, bénéficie d'un scanner thoracique non injecté pour référencer le positionnement de chaque électrode thoracique par rapport à la géométrie cardiaque. Des coupes de 3mm espacées de 1.5mm sont réalisées avec une dose efficace pour le patient d'environ 4.5mSv (3 fois moins qu'un angio-scanner thoracique). Habituellement les images sont indexées sur l'onde R pour l'obtention des volumes diastoliques adaptés à la reconstruction de l'activation. Il est possible, pour la réalisation de cartes de repolarisation, d'indexer les images sur l'onde T et d'acquérir des volumes systoliques. La géométrie cardiaque et le positionnement des électrodes sont segmentés sur chaque coupe transverse et une relation cœur-surface thoracique est établie dans un référentiel tridimensionnel.

Traitement du signal

Les électrogrammes de surfaces et la géométrie cardiaque sont ensuite traités suivant différentes étapes :

- prétraitement des signaux électrocardiographiques par filtration du bruit, correction de la ligne de base, élimination des signaux imparfaits (défaut de contact) et interpolation des signaux manquants.
- traitement des images par des algorithmes de segmentation (oreillettes et ventricules sont segmentés séparément) et maillage des surfaces cardiaque et thoracique (triangulation linéaire).
- résolution du problème inverse ; la méthode des éléments frontières est utilisée pour discrétiser l'équation de Laplace et obtenir ainsi la relation linéaire : $V_T = AV_E$; V_E étant le vecteur des potentiels épicaux, V_T le vecteur des potentiels thoraciques et A, la matrice de transfert (qui dépend de la géométrie et de la conductivité du conducteur

thoracique). Avec la méthode des éléments frontières, la conductivité du milieu est supposée homogène et isotropique.^{33,34} L'équation ci-dessus représente le problème direct : définir les potentiels de surface thoraciques à partir des potentiels épicaudiques. La résolution du problème inverse ne peut se limiter à l'inversion de cette équation ; en effet, il s'agit d'un problème « mal posé » (ill-posed). Ceci signifie qu'un faible niveau de bruit dans les mesures peut induire des erreurs majeures de reconstruction. Pour pallier à cela, il est nécessaire d'ajouter des contraintes ou des *a priori* qui permettent de réduire l'espace des possibilités pour la solution : on appelle cela la régularisation. L'ECM utilise une régularisation spatiale et temporelle selon les méthodes de Tikhonov et de résidu minimal généralisé.³⁵

- le post traitement permet sur un cycle cardiaque la réalisation : 1/ de cartes de potentiels révélant la distribution spatiale des potentiels sur le cœur en 3D, ces cartes étant disponibles sur l'ensemble du cycle cardiaque à un échantillonnage de 1ms. 2/de cartes d'isochrones imageant la séquence d'activation épicaudique basée sur le temps d'activation local, défini par le maximum de la dérivée négative du signal unipolaire ($-dV/dt_{\max}$) référencé au début du QRS (onde Q ou spike de stimulation). 3/des cartes de voltage et des cartes de repolarisation.

Une séquence complète d'activation ne nécessite qu'un cycle cardiaque ce qui permet en quelques secondes l'acquisition de plusieurs cartes d'activation dans des conditions différentes (activation spontanée, activation stimulée, différents modes de stimulation).

Etudes de validation

Les premières études de validation chez l'animal ont fait appel à un modèle de cœur isolé-perfusé de chien équipé d'électrodes épicaudiques immergé dans un contenant thoracique recouvert lui aussi d'électrodes. La cartographie électrocardiographique a ainsi été testée sur cœur sain, en condition d'activation spontanée et de stimulation cardiaque (mono et multipoints).^{29,36} Sur le même modèle, l'ECM a été évalué sur cœur ischémique ainsi qu'en condition d'arythmie ventriculaire.³⁷⁻³⁹ Dans ces différentes études, l'ECM était capable de reconstruire les électrogrammes épicaudiques avec un phénomène d'atténuation en amplitude mais néanmoins des coefficients de corrélation croisée avec des électrogrammes

mesurés à la surface du cœur de l'ordre de 90% avec une résolution spatiale de l'ordre de 10 mm. Ces études n'étaient réalisées que sur un nombre limité d'animaux (un animal unique pour chaque étape de validation).

Chez l'homme, l'ECM a été utilisé pour décrire l'activation ventriculaire spontanée, l'activation avec bloc de branche droit, l'activation induite par la stimulation ventriculaire droite, ainsi que pour la description d'un circuit de flutter commun.^{32,40} Ghanem et co ont présenté en 2005 une étude de validation humaine comparant les électrogrammes reconstruits à des électrogrammes obtenus à l'aide de patchs cardiaques d'électrodes temporaire appliqués lors d'une chirurgie cardiaque (2x100 électrodes).⁴¹ Trois patients ont été inclus dans cette étude, pour totaliser 5 séquences d'acquisition : 2 en rythme spontané, 2 en stimulation VD épicardique et 1 en stimulation VD endocardique. Les coefficients de corrélation croisés étaient en rythme spontané voisin de 0.85 pour la face antérieure du cœur, 0.60 pour la face postérieure avec un délai temporel d'environ 7 à 10 ms. Pour la stimulation epicardique, le coefficient de corrélation moyen était de 0.71 avec un délai temporel voisin de 20 ms. La précision de localisation du site de stimulation était de 16 mm, et 19 mm en dépit du fait que les acquisitions (invasive et non-invasive) aient été réalisées l'une à thorax ouvert, l'autre à thorax fermé et décalées dans le temps. Plus récemment l'ECM a fait l'objet d'une évaluation dans le diagnostic des arythmies atriales focales ou macro-réentrantes.⁴² Sur 48 patients, le mécanisme et la localisation de l'arythmie diagnostiqués par ECM étaient comparés aux données de la cartographie de contact et de la procédure d'ablation. Le diagnostic ECM était validé dans 100% des arythmies atriales de novo et 82% des arythmies post-ablation.

Limites

En comparaison des données de cartographie invasive de contact, il semble que l'amplitude des électrogrammes reconstruits par ECM soit moindre. Ce phénomène est potentiellement en rapport avec l'utilisation de la méthode des éléments frontières qui fait abstraction de l'inhomogénéité du conducteur thoracique (constitué par les poumons, le sang, les vaisseaux, les fluides, les os).^{34,41}

Lignes de conduction lente

Une des spécificités de ce type de système de cartographie non invasive est de mettre en évidence dans certaines conditions des lignes de conduction lente définies dans la littérature comme des lignes de bloc.^{43,44} Nous avons défini dans ce travail une ligne de conduction lente lorsque deux points de part et d'autre de la ligne différaient dans leurs temps d'activation de plus de 50 ms (figure 3 et 4). La plupart de ces lignes ont un caractère fonctionnel, disparaissant à la faveur d'une modification de la séquence d'activation ventriculaire (stimulation par exemple). De longues lignes de conduction lente (comme décrites dans le BBG ou la stimulation ventriculaire) sont évocatrices d'un phénomène de conduction myocardique de cellule à cellule. Elles sont typiquement parallèles au front d'activation et dans le BBG d'orientation baso-apicale. La figure 3 représente une ligne de conduction lente chez un patient avec BBG. Les EGM épicaudiques ont été numérotés de 1 à 7 et correspondent aux points de couleur sur la carte (de gauche à droite). Les EGM les plus éloignés, 1 et 7 présentent une pente négative claire avec une $-dV/dt_{\max}$ précisément identifiée (barre verticale blanche sur l'EGM). De part et d'autre de la ligne, les EGM adjacents 3 et 4 présentent des caractéristiques communes aux EGM éloignés 1 et 7 avec plusieurs pentes négatives. Entre 3 et 4, l'ECM calcul et indique la $-dV/dt_{\max}$ à deux endroits différents espacés dans le temps de 54 ms. Ce saut de marquage de la $-dV/dt_{\max}$ est ainsi responsable de l'aspect de ligne et du changement abrupt de couleur (vert à bleu) sur la carte. Il est probable que cet aspect de ligne soit artificiel, ne correspondant pas à un bloc de conduction vrai. En revanche, au niveau de cette zone, la vélocité de conduction présente un ralentissement marqué (transition rapide entre 1 et 7). Les données de cartographie de contact chez l'homme corroborent cette hypothèse : Wyndham et co décrivent de telles zones de ralentissement en régions paraseptales antérieure et postérieure chez 5 patients avec BBG lors d'une chirurgie de pontage aorto coronarien.⁴⁵

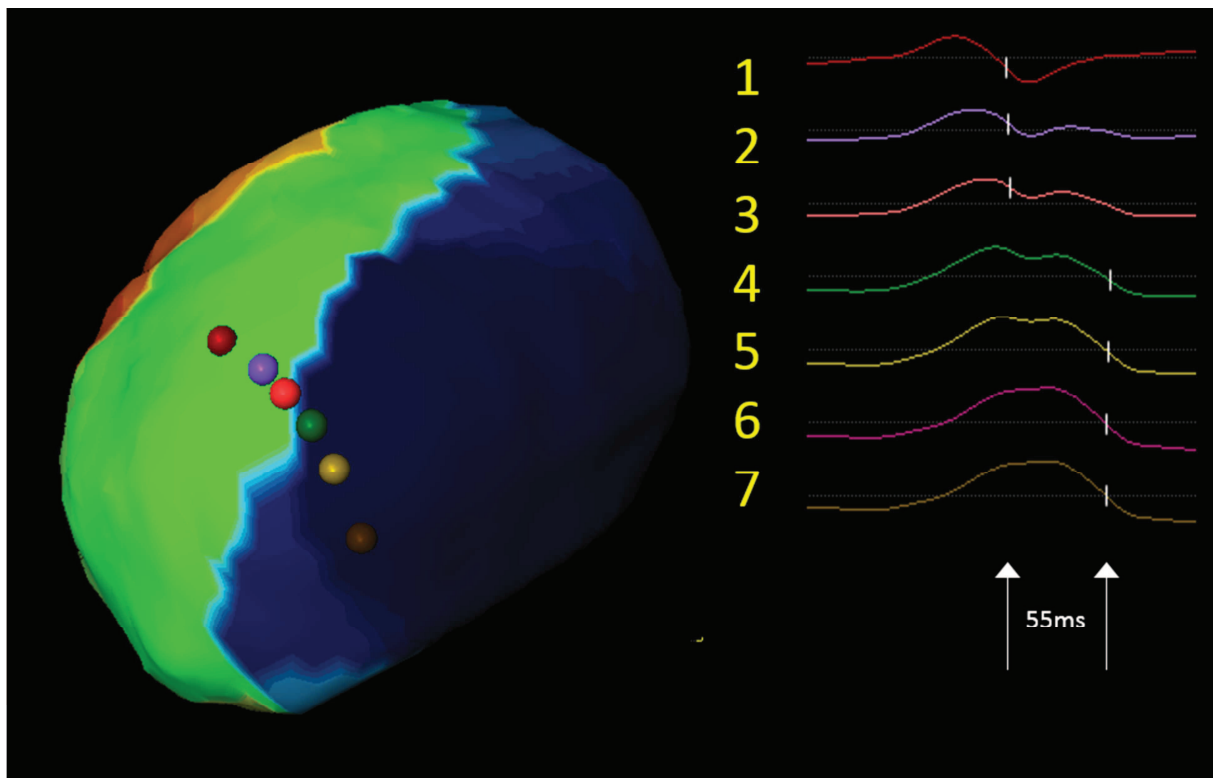


Figure 3 : Exemple de ligne de conduction lente fonctionnelle dans le BBG. Il y a une correspondance de couleur entre les EGM numérotés de 1 à 7 et les points représentés sur la carte. Voir texte.

En plus des lignes de conduction lente fonctionnelles, on observe plus rarement des zones de conduction lente dépendantes du substrat anatomique. Ces zones prennent l'aspect de lignes courtes sans orientation particulière par rapport au front d'activation. Ces zones sont en général peu étendues, et ont un impact important sur les différentes séquences d'activation. La figure 4 représente une telle zone de conduction lente isolée sur la paroi latérale du VD (patient avec BBG). Dans cet exemple on voit que les EGM 1 et 2 ont un aspect QS typique d'une activation précoce, le temps d'activation calculé à partir de la $-dV/dt_{\max}$ est court. La courbe de conduction lente circonscrit une zone de bas voltage avec une activation retardée (îlot bleu avec EGM 4, 5, 6). Entre les EGM 3 et 4 on mesure 74 ms, dans ce cas il est probable que cette ligne corresponde à une vraie ligne de bloc, forçant l'activation à contourner cet obstacle par la gauche (transition vert-bleu).

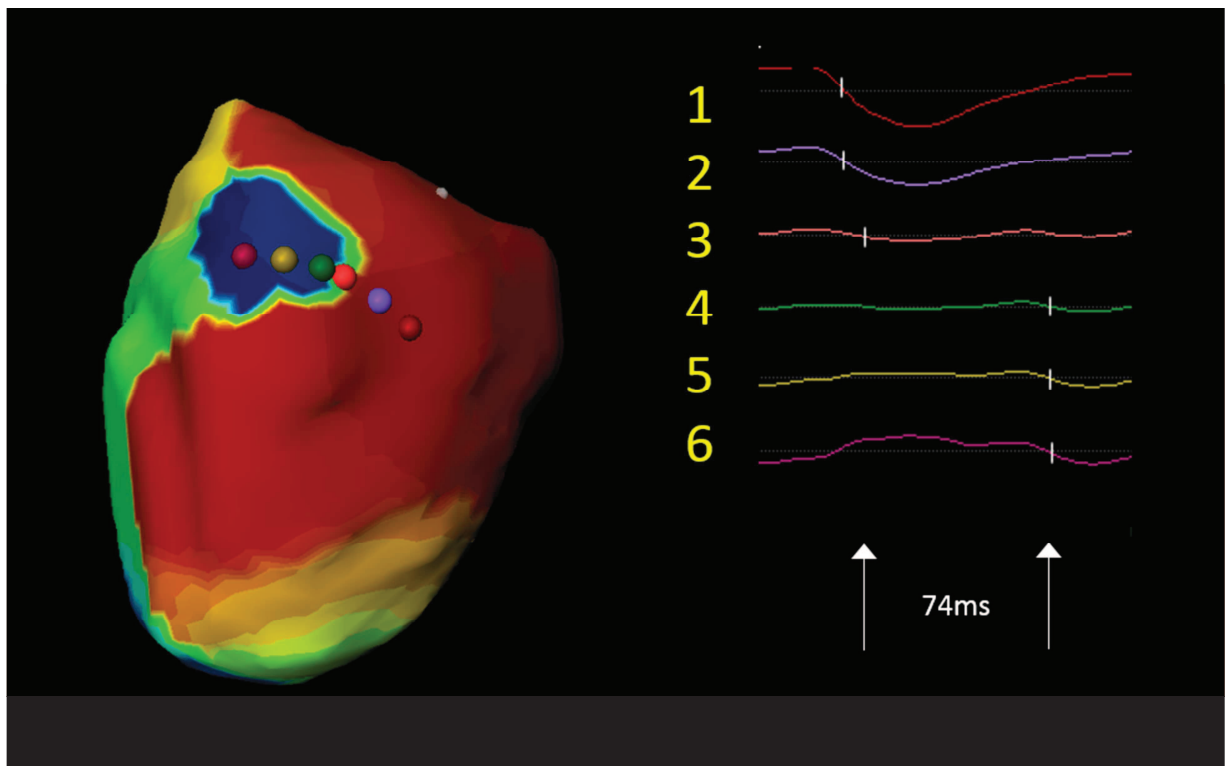


Figure 4 : Exemple de ligne de conduction lente non-fonctionnelle sur la paroi latérale du VD. Il y a une correspondance de couleur entre les EGM numérotés de 1 à 6 et les points représentés sur la carte. Voir texte.

ECM et asynchronisme cardiaque

Dans un premier article, Jia et co ont présenté les cartes d'activation non invasives de six patients avec BBG, en rythme spontané, stimulé sur le VD, le VG et en BIV. Ils ont proposé un index d'asynchronisme Esyn défini comme la différence entre les temps d'activation moyen des parois latérales VD et VG. Plus cet index est négatif, plus la paroi latérale VG est retardée dans son activation par rapport à la paroi latérale VD. Ils ont montré que la stimulation BIV minimise Esyn qui passe de -76ms en rythme spontané à -20ms en BIV. Un autre index d'asynchronisme a été proposé par Ghosh et co : ED définit comme l'écart type du temps d'activation VG (environ 500 points).⁴⁶ Cet indice n'était pas corrélé à la durée du QRS, mais la stimulation BIV réduisait significativement ED chez les 18 patients répondeurs (remodelage VG).

Dans ce travail, nous avons principalement utilisé les données d'activation à partir desquelles nous avons défini de nouveaux indices d'asynchronisme :

- TAT (Total Activation Time): le temps total d'activation ventriculaire (VD+VG épicaordique) défini comme la différence entre le temps d'activation ventriculaire maximum et le temps d'activation ventriculaire minimum (en ms).
- LVTAT (Left Ventricular Total Activation Time): le temps total d'activation VG (épicaordique) défini comme la différence entre le temps d'activation VG maximum et le temps d'activation VG minimum (en ms).
- RVTAT (Right Ventricular Total Activation Time): le temps total d'activation VD (épicaordique) défini comme la différence entre le temps d'activation VD maximum et le temps d'activation VD minimum (en ms).
- VEU : (Ventricular Electrical Uncoupling) défini comme la différence des temps d'activation moyens entre les deux ventricules. Un VEU positif correspond à un retard d'activation du VG par rapport au VD et inversement. Plus le VEU est large, plus les ventricules sont « découplés » dans leurs activations relatives.

5 LA MODELISATION CARDIAQUE NUMERIQUE : CIRCAdAPT MODEL.

Dans une étude présentée dans ce travail, nous avons combiné expérimentations chez l'homme, expérimentations chez l'animal et données en provenance d'un modèle informatique, le CircAdapt. Ce modèle, développé par l'équipe du professeur Arts de l'université de Maastricht, permet d'évaluer la mécanique et l'hémodynamique cardiaque en réponse à un certain nombre de conditions physio(patho)logique telles que la perte de contractilité (segmentaire ou globale), la fibrose, les pathologies valvulaires ou les différences d'activation.⁴⁷ Ce modèle est donc particulièrement adapté à notre thématique: effets délétères de l'asynchronisme ventriculaire et effets favorables de la resynchronisation BIV.

Ce modèle informatique est basé sur la relation et l'interdépendance de différents modules : les chambres cardiaques, les valves, les tubes et les résistances. Oreillettes et ventricules sont composés de tissu contractile (voir ci-dessous) dont la pression interne dépend du volume des

cavités. Les gros vaisseaux sont modélisés par des modules de tubes élastiques non linéaires (courbe pression-compliance non linéaire) avec une impédance caractéristique pour la propagation du flux pulsatile. Tubes et chambres sont connectés par des valves dotées d'inertie et répondant au théorème de Bernoulli. Le diamètre de la valve dépend de la direction et de l'amplitude du flux qui la traverse ainsi que de la chute de pression d'aval. Les lits systémique et pulmonaire périphériques sont représentés par des résistances non linéaires connectant les artères systémiques et pulmonaires aux veines. L'agencement de ces différents modules est représenté dans la figure 5 A.

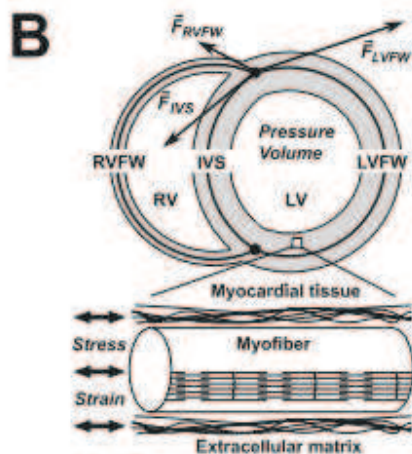
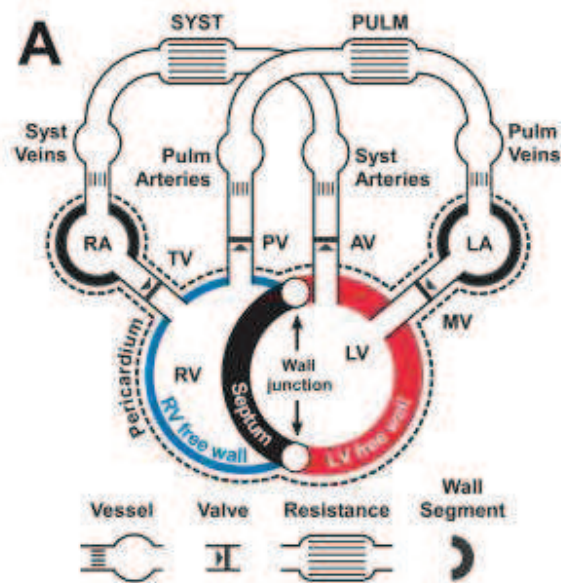
Les ventricules ont une architecture initialement tri-segmentaire avec un septum et deux murs ventriculaires libres droit et gauche définissant ainsi 2 ventricules (voir figure 5 B).⁴⁸ L'interaction mécanique des deux ventricules obéit à la loi d'équilibre des forces aux points de jonction des segments ($\dot{F}_{VG} + \dot{F}_{VD} + \dot{F}_{sept} = 0$). Chaque segment est modélisé selon un modèle musculaire à 3 composantes (Hill): la composante contractile (ponts actine-myosine), la composante élastique en série (active au niveau des ponts et passive dépendante des tendons) et la composante élastique en parallèle (tissu conjonctif, sarcolemme). Le travail global de chaque ventricule (boucle pression volume) est relié au travail segmentaire (boucle stress-strain) par le principe de conservation du travail.

Ce modèle propose également une adaptation structurelle des vaisseaux et segments musculaires aux variations de condition de charge. Cette composante devrait permettre dans le futur, de prédire les effets au long cours d'un mode de stimulation en fonction de l'état basal en rythme spontané.

Au final, le modèle génère des courbes de paramètres hémodynamiques et mécaniques en fonction du temps sur l'intégralité du cycle cardiaque : pressions vasculaires, cardiaques, flux trans-valvulaire, courbes stress-strain ... La simulation d'un cycle cardiaque prend en moyenne moins de 4 secondes. Ce modèle a été validé par différentes études comparant données réelles observées chez l'homme ou chez l'animal et données fournies par le modèle. Pour la thématique de l'insuffisance cardiaque et de l'impact de la séquence d'activation électrique, ce modèle s'est avéré capable de simuler avec une grande fiabilité l'hémodynamique cardiaque en

conditions d'hypertension artérielle pulmonaire ainsi qu'en conditions d'asynchronisme ventriculaire induit par un BBG.^{5,49,50}

Une version simplifiée, libre de droit à destination d'enseignement est disponible à l'adresse internet suivante : <http://www.circadapt.org/>.



FORCE EQUILIBRIUM IN JUNCTION:

$$\vec{F}_{LVFW} + \vec{F}_{IVS} + \vec{F}_{RVFW} = 0$$

CONSERVATION OF WORK:

$\int_{\text{Cardiac cycle}} \text{Pressure}_{LV} \times \Delta \text{Volume}_{LV}$	$\int_{\text{Cardiac cycle}} \text{Stress}_{LVFW} \times \Delta \text{Strain}_{LVFW}$
$\int_{\text{Cardiac cycle}} \text{Pressure}_{RV} \times \Delta \text{Volume}_{RV}$	$\int_{\text{Cardiac cycle}} \text{Stress}_{IVS} \times \Delta \text{Strain}_{IVS}$
	$\int_{\text{Cardiac cycle}} \text{Stress}_{RVFW} \times \Delta \text{Strain}_{RVFW}$
+	+
TOTAL PUMP WORK	= TOTAL MYOFIBER WORK

Figure 5 A : Représentation schématique de l'agencement des différents modules du modèle CircAdapt. **B :** Représentation schématique du myocarde selon 3 segments. D'après²².

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RESULTATS

7 IMPACT SUR LA $dp/dt_{max}VG$ DE LA STIMULATION BIVENTRICULAIRE CHEZ DES PATIENTS INSUFFISANTS CARDIAQUES PRESENTANT DES QRS FINS, MODEREMENT OU SEVEREMENT ELARGIS.*

*Ploux S, Whinnett Z, Lumens J, Denis A, Zemmoura A, De Guillebon M, Ramoul K, Ritter P, Jaïs P, Clementy J, Haïssaguerre M, Bordachar P: Acute hemodynamic response to biventricular pacing in heart failure patients with narrow, moderately, and severely prolonged QRS duration. *Heart Rhythm Off J Heart Rhythm Soc* 2012.

7.1 INTRODUCTION:

Il est démontré que la CRT améliore l'hémodynamique aigue ainsi que la symptomatologie et la survie des patients insuffisants cardiaques présentant une altération de la fraction d'éjection et un élargissement du QRS de surface. Au-delà de 120ms il semble exister une relation entre l'amélioration hémodynamique aigue et la largeur du QRS de base.¹⁴ En émettant l'hypothèse d'une relation directe entre asynchronisme électrique (défini par la largeur du QRS) et amélioration hémodynamique sous l'impulsion d'une stimulation BIV, les patients à QRS dits fins (<120ms) de devraient pas tirer de bénéfice. Plusieurs études cependant vont démontrer un bénéfice hémodynamique ou clinique de la CRT dans ce groupe, similaire à celui observé pour les patients à QRS larges.⁵²⁻⁵⁷ Bleeker et co. retrouve un degré d'asynchronisme mécanique intra-VG (évalué par echo-doppler tissulaire) similaire pour les patients a QRS fins (n=33) et larges (n=33), résultant en une diminution équivalente de la classe NYHA et du volume télésystolique VG à 6 mois.⁵⁸ La même équipe va remettre en cause la validité de la durée du QRS comme critère d'asynchronisme sur une population de patients à QRS larges. Pourtant, le seul essai randomisé contrôlé ayant évalué l'efficacité de la CRT chez les patients à QRS fins s'est avéré négatif (proportion similaire de patient ayant amélioré leur pic de VO_2 à six mois, par rapport au groupe contrôle). Le but de notre étude était de démontrer qu'il existe une relation entre l'asynchronisme électrique (mesuré par la durée du QRS) et l'amélioration hémodynamique induite par la stimulation BIV. Pour tester cette hypothèse nous avons mesuré de façon invasive les modifications de $dp/dt_{max}VG$ induite par la stimulation BIV dans une

population de patients insuffisants cardiaque (n=82) présentant une large gamme de durée de QRS (de fin à très large).

7.2 RESULTATS :

Nous avons mis en évidence une corrélation significative entre la durée du QRS mesurée sur l'ECG de surface et le pourcentage de modification de la $dP/dt_{\max}VG$ (en référence à la conduction spontanée) induite par la stimulation BIV : $r=0.65$, $p<0.001$. Selon l'analyse ROC (aire sous la courbe 0.82; IC à 95% [0.72–0.94]; $P<0.001$) une amélioration $\geq 10\%$ de la $dP/dt_{\max}VG$ peut être prédite au seuil de 141ms de durée de QRS avec une sensibilité de 90% et une spécificité de 75%. La stimulation BIV entraînait une augmentation moyenne de $dP/dt_{\max}VG$ de $14.2\pm 13.3\%$ par rapport à la référence dans le groupe de patients à QRS large ($>120ms$) alors que les patients à QRS fins ne tiraient aucun bénéfice : $0.4\pm 6.1\%$, $p=ns$.

Cette étude démontre qu'il existe une relation étroite entre asynchronisme électrique et réponse hémodynamique à la CRT. La durée du QRS est un paramètre d'asynchronisme électrique valide pour la sélection des candidats à la CRT. Une analyse plus détaillée de l'asynchronisme par cartographie d'activation électrique devrait permettre d'améliorer cette relation et ainsi la sélection des candidats à la CRT.

Acute hemodynamic response to biventricular pacing in heart failure patients with narrow, moderately, and severely prolonged QRS duration

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BACKGROUND The efficacy of biventricular (BiV) pacing in patients with a narrow or moderately prolonged QRS duration remains questionable.

OBJECTIVE To assess the hypothesis that electrical dyssynchrony is required to obtain hemodynamic benefit from BiV pacing by investigating the relationship between intrinsic QRS duration and hemodynamic response to BiV pacing in a patient population covering a broad spectrum of QRS duration.

METHODS Eighty-two consecutive heart failure patients underwent cardiac resynchronization therapy implantation irrespective of their QRS duration. Thirty-four patients had a narrow QRS duration (<120 ms), whereas 11 patients had a moderately prolonged QRS duration (≥120 to <150 ms) and 37 patients had a severely prolonged QRS duration (≥150 ms). After implantation, invasive left ventricular (LV) dP/dt measurements were compared between intrinsic rhythm and simultaneous BiV pacing with an optimized atrioventricular delay.

RESULTS A high correlation ($r = .65$; $P < .001$) was observed between baseline QRS duration and changes in LV dP/dt_{max} induced by BiV pacing. BiV pacing was ineffective in patients with

a narrow QRS duration ($+0.4\% \pm 6.1\%$; $P = \text{ns}$). No significant increase in LV dP/dt_{max} was observed in patients with a QRS duration of ≥120 to <150 ms ($+4.4\% \pm 6.9\%$; $P = .06$), whereas patients with a QRS duration of ≥150 ms exhibited a significant increase in LV dP/dt_{max} ($+17.1\% \pm 13.4\%$; $P < .001$). Only 9% of the patients with a narrow QRS duration exhibited a ≥10% increase in LV dP/dt_{max}.

CONCLUSIONS Baseline QRS duration is linearly related to acute hemodynamic response to BiV pacing. Patients with a narrow QRS duration do not derive hemodynamic improvement. This improvement is also limited in patients with a moderately prolonged QRS duration, raising questions about the potential clinical benefit of this therapy in these patients.

KEYWORDS Cardiac resynchronization therapy; QRS; Biventricular pacing; Narrow QRS; Hemodynamic

ABBREVIATIONS AV = atrioventricular; BiV = biventricular; CRT = cardiac resynchronization therapy; LV = left ventricular (Heart Rhythm 2012;9:1247–1250) © 2012 Heart Rhythm Society. All rights reserved.

Introduction

Many acute hemodynamic response studies and large randomized outcome trials have provided evidence that cardiac resynchronization therapy (CRT) improves cardiac hemodynamics, symptoms, and life expectancy of patients with chronic heart failure, decreased left ventricular (LV) ejection fraction (<35%), and a wide QRS complex (≥120 ms).^{1–6} The surface electrocardiogram is currently the only recommended and validated tool used for selecting candidates for CRT.^{7,8} In patients with a wide QRS complex (≥120 ms), hemodynamic response to CRT has been demonstrated to be related to the baseline QRS duration; that is,

the wider the QRS complex, the larger the response.⁹ Considering this relationship, one would expect limited response to CRT in patients with a narrow QRS duration (<120 ms). However, 4 recent studies including only patients with a narrow QRS duration demonstrated unexpectedly positive hemodynamic response to CRT, questioning the direct relationship between QRS duration and hemodynamic response.^{10–13} There is no study yet that analyzed this relationship in a patient population covering the full range of QRS duration, allowing head-to-head comparison of patients with narrow vs wide QRS. Moreover, questions remain regarding the efficacy of biventricular (BiV) pacing in patients with a narrow QRS duration, since the only large multicenter randomized clinical trial was concluded negative.¹⁴

In this study, we hypothesized that electrical dyssynchrony is required to obtain hemodynamic benefit from

Dr Ploux received financial support from the Fédération Française de Cardiologie. Dr Whinnett was funded by the British Heart Foundation (FS/09/048/28011). **Address for reprint requests and correspondence:** Dr Sylvain Ploux, MD, Hôpital Cardiologique Haut Leveque, Bordeaux-Pessac 33604, France. E-mail address: sylvain.ploux@free.fr.

CRT. To assess this hypothesis, we investigated the relationship between intrinsic QRS duration and hemodynamic response to BiV pacing in a broad spectrum of heart failure patients, including patients with narrow, moderately prolonged, and severely prolonged QRS durations.

Methods

Patient population

The study enrolled 82 consecutive patients who fulfilled the following criteria: (1) New York Heart Association functional class II to IV despite optimal medical therapy and (2) LV ejection fraction of $\leq 35\%$ during sinus rhythm. All patients who fulfilled the above-mentioned criteria were included in the study, irrespective of their QRS duration. Echocardiographic measurements of dyssynchrony were not used for patient selection. The presence of a third-degree atrioventricular block, severe aortic valve stenosis, or LV intracavitary thrombus were criteria for exclusion. Overall, 34 patients with a narrow QRS duration (<120 ms) and 48 patients with a wide QRS duration (11 patients with a moderately prolonged QRS duration [≥ 120 to <150 ms] and 37 patients with a severely prolonged QRS duration [≥ 150 ms]) were included. Their mean age was 64 ± 11 years, 67 were men (82%), 41 (50%) had an ischemic cardiomyopathy, 24 (29%) were in New York Heart Association class II, 55 (67%) were in class III, and 3 (4%) were in class IV. The mean LV ejection fraction was $27\% \pm 5\%$. The mean QRS duration was 140 ± 36 ms, 34 patients presented a left bundle branch block, and 2 presented a right bundle branch block.

Protocol for the implantation of the CRT device

All patients were implanted with a CRT-defibrillator device with the leads placed via the standard percutaneous transvenous approach. Anterior location was discouraged for LV lead positioning. All patients had a lead placed at the right ventricular apex and in the right atrium.

Acute hemodynamic studies

In the 72 hours following CRT device implantation, a Radi pressure micromanometer (Radi Medical Systems, St Jude Medical, St Paul, MN) was placed in the LV cavity via retrograde transaortic catheterization through the radial artery. This allowed the instantaneous and continuously calibrated recording of LV pressure, dP/dt_{\max} and dP/dt_{\min} . Each measurement represented the mean of a 10-second recording, ensuring that this was free from ventricular or supraventricular extrasystoles. Pressure data were recorded after a 30-second period to allow hemodynamic stabilization. In all patients, we performed hemodynamic measurements during sinus rhythm and during atrial-sensed BiV stimulation (VDD). For each pacing configuration, hemodynamic response was defined by the percentage change in $LV\ dP/dt_{\max}$ relative to the closest baseline measurement (ie, spontaneous rhythm); baseline measurements were repeated every 4 acquisitions. During BiV pacing, multiple atrioventricular (AV) delays were tested in a random order

in steps of 20 ms and starting from 60 ms. The longest tested AV delay was the longest one providing complete capture without fusion with intrinsic rhythm (defined as any changes in the width or morphology of the QRS on the surface electrocardiogram). We defined the optimal AV delay as the one providing the highest $LV\ dP/dt_{\max}$ improvement. A positive hemodynamic response was defined as a $\geq 10\%$ increase in $LV\ dP/dt_{\max}$ for the analysis.

Statistical analysis

The data are presented as means \pm standard deviation. All statistical comparisons were performed by using the CRT responses obtained at the optimal AV delay for each patient. Correlations between changes in $LV\ dP/dt_{\max}$ and baseline QRS duration were evaluated by linear regression analysis. Optimal cutoff value of QRS duration with regard to the prediction of CRT response (dichotomous response scale: hemodynamic responder defined by $\geq 10\%$ increase in $LV\ dP/dt_{\max}$) was determined by constructing a receiver operating characteristics curve. Optimal cutoff value was selected where the sum of sensitivity and specificity was maximal in the receiver operating characteristics analysis. Hemodynamic response to BiV pacing was compared with that at baseline by using a 2-tailed, paired Student *t* test. Mean hemodynamic response in the narrow QRS group (<120 ms) was compared with that of the wide QRS group (≥ 120 ms) by using a 2-tailed Student *t* test. The same strategy was applied for the comparison within the wide QRS group between patients with a QRS duration of ≥ 120 to <150 ms and patients with a QRS duration of >150 ms. Response rates of the different QRS groups were compared by using the Pearson χ^2 test or the Fisher exact test. Statistical significance was defined by a *P* value of $<.05$. All statistical analyses were performed by using the SPSS software, version 17.0 (SPSS, Inc, Chicago, IL).

Results

Relationship between QRS duration and acute hemodynamic response

We observed a significant relationship between baseline QRS duration and the acute hemodynamic response to BiV pacing. Acute hemodynamic response increased linearly with baseline QRS duration ($r = .65$; $P < .001$) (Figure 1). Receiver operating characteristics analysis revealed that a QRS duration of ≥ 141 ms identified hemodynamic responders defined by a $\geq 10\%$ increase in $LV\ dP/dt_{\max}$ with 90% sensitivity and 75% specificity (area under the curve 0.82; 95% confidence interval 0.72–0.94; $P < .001$).

Comparison in hemodynamic response between patients with narrow or wide QRS

In the wide QRS group (≥ 120 ms), BiV pacing resulted in a $14.2\% \pm 13.3\%$ increase in $LV\ dP/dt_{\max}$ with respect to baseline, whereas no significant improvement was observed in the narrow QRS group ($+0.4\% \pm 6.1\%$ vs baseline; $P = ns$). Overall, hemodynamic response was larger in the wide QRS group than in the narrow QRS group ($P < .001$). At a

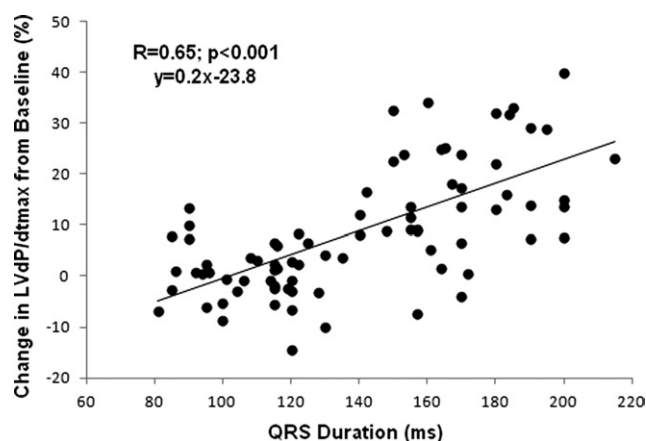


Figure 1 Correlation between baseline QRS duration and changes in LV dP/dt_{max} induced by biventricular stimulation compared with spontaneous rhythm. LV = left ventricular.

$\geq 10\%$ -level increase in LV dP/dt_{max} , 9% of the patients with narrow QRS were found responders whereas 54% of the patients with wide QRS did respond to BiV pacing ($P < .001$) (Figure 2).

Subgroup analysis within the wide QRS group

Of the 48 patients with wide QRS, 11 had a QRS duration of ≥ 120 to < 150 ms (moderately prolonged) and 37 had a QRS duration of ≥ 150 ms (severely prolonged). In the latter group, BiV stimulation significantly increased LV dP/dt_{max} ($+17.1\% \pm 13.4\%$; $P < .001$ vs baseline). In contrast, no significant LV dP/dt_{max} change was observed for the patients with a moderately prolonged QRS duration ($+4.4\% \pm 6.9\%$; $P = .06$ vs baseline). Overall, hemodynamic response to BiV pacing was significantly larger for patients with a severely prolonged QRS duration than for those with a moderately prolonged QRS duration ($P = .004$). Only 9% of the patients with a moderately prolonged QRS duration were found to be hemodynamic responders compared with 68% of the patients with a severely prolonged QRS duration ($P < .001$).

Discussion

In this study, we report several observations that have clinical implications. First, we demonstrated a linear relationship between intrinsic QRS duration and hemodynamic response to BiV pacing in a cohort of heart failure patients including patients with both narrow and wide QRS durations. Second, patients with a narrow QRS duration did not obtain significant hemodynamic benefit from conventional BiV pacing. Third, patients with a significantly prolonged QRS duration (≥ 150 ms) derived greater benefit from CRT than did those with a moderately prolonged QRS duration (≥ 120 to < 150 ms).

Relationship between baseline QRS duration and acute hemodynamic response to CRT

To the best of our knowledge, this is the first study that reports a linear relationship between QRS duration and acute hemodynamic response to CRT when tested across a wide range of baseline QRS durations from normal to very prolonged. This finding is consistent with the results of clinical outcome studies conducted in patients with a wide QRS duration (≥ 120 ms), in which the baseline QRS duration has been shown to be associated with clinical response to BiV pacing.¹⁵

Response to conventional CRT in patients with a narrow QRS duration

We found no beneficial acute hemodynamic effect as a result of conventional CRT in an unselected group of patients with a narrow QRS duration. We believe that this finding implies that this group of patients is unlikely to gain long-term clinical benefit from BiV pacing. Our findings differ from those obtained in a recent hemodynamic study focusing on patients with a narrow QRS duration without echocardiographic evidence of dyssynchrony.¹³ In this study, Williams et al¹³ reported highly favorable short-term hemodynamic results with standard BiV pacing, including a $9\% \pm 2\%$ significant increase in LV dP/dt_{max} . The patients in our study had very similar clinical characteristics, the most obvious difference being that we included all patients

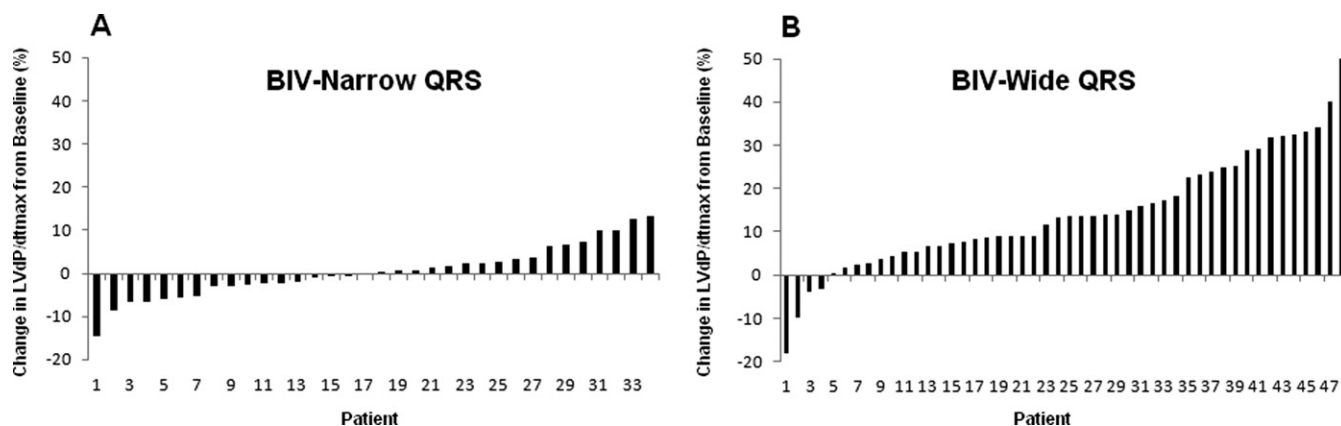


Figure 2 Distribution patient by patient of LV dP/dt_{max} changes from baseline to biventricular (BiV) pacing, in patients with a narrow QRS duration (A) and a wide QRS duration (B).

with a baseline narrow QRS duration, whereas only patients with *no echocardiographic evidence* of mechanical dyssynchrony were included in the aforementioned study. It is unexpected that a positive hemodynamic response was observed only in the group of patients in whom there was no evidence of mechanical dyssynchrony; it may be that there are in fact other differences between the patient groups that are not immediately apparent.

In contrast, we did identify clear improvements in LV dP/dt_{max} in patients with a broad baseline QRS duration (≥ 120 ms); these improvements were of a similar magnitude to those seen in other acute hemodynamic studies.^{2,16,17}

These 2 findings demonstrate that an electrical substrate is a prerequisite for CRT effectiveness.

The patient population with a moderately prolonged QRS duration

Subgroup analysis of the clinical outcome trials comparing patients with a QRS duration between 120 and 150 ms and patients with a QRS duration of >150 ms have consistently shown a greater clinical benefit for those in the latter group.^{5,18–21} On the basis of this observation, the professional societies introduced in their most recent guidelines the cutoff value of 150 ms for the patients with mild to moderate heart failure.^{7,22} For the Heart Failure Society of America, CRT is no more recommended but “may be considered” for patients with a QRS duration of ≥ 120 to <150 ms (strength of evidence B). For the European Society of Cardiology, CRT is still recommended in this population with New York Heart Association III–IV (class I, level A). In agreement with this trend to restrict CRT to patients with the higher probability of response, our data suggest that patients with a moderately prolonged QRS duration are less likely to respond than those with a QRS duration of ≥ 150 ms.

Study limitations

We used acute change in LV dP/dt_{max} as our outcome measure rather than clinical response. CRT was shown to improve acute hemodynamics in patients with a broad QRS duration prior to carrying out the larger outcome studies that subsequently demonstrated improvements in clinical outcomes. Moreover, the relationship between acute hemodynamic response and reverse LV remodeling has recently been demonstrated.²³

Conclusions

Baseline QRS duration is linearly related to acute hemodynamic response to BiV pacing. Patients with a narrow QRS duration (<120 ms) do not obtain hemodynamic benefit from CRT. Patients with a significantly prolonged QRS duration (≥ 150 ms) derived greater benefit from CRT than did those with a moderately prolonged QRS duration (≥ 120 to <150 ms), raising questions about the potential clinical benefit of this therapy for the latter.

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8 LA CARTOGRAPHIE D'ACTIVATION NON INVASIVE ELECTROCARDIOGRAPHIQUE (ECM) POUR AMELIORER LA SELECTION DES CANDIDATS A LA CRT : AU-DELA DE LA DUREE DU QRS OU L'ASPECT DE BLOC DE BRANCHE GAUCHE.*

*Ploux S, Lumens J, Whinnett Z, et al. Noninvasive electrocardiographic mapping to improve patient selection for cardiac resynchronization therapy: beyond QRS duration and left bundle branch block morphology. *J Am Coll Cardiol* 2013

8.1 INTRODUCTION:

La sélection des patients candidats à la CRT basée sur la durée du QRS ($\geq 120\text{ms}$) s'accompagne d'un incompressible taux de non répondeur à la resynchronisation d'environ 30%. Les espoirs suscités par l'évaluation mécanique (échocardiographique principalement) de l'asynchronisme ont été finalement déçus entraînant un regain d'intérêt pour l'évaluation électrique de l'asynchronisme.²¹ La morphologie de BBG sur l'ECG de surface est identifiée comme la meilleure image du substrat favorable à la CRT alors que BBD et troubles de conduction aspécifiques (NICD) a contrario apparaissent comme de mauvais candidats en dépit de l'élargissement du QRS qu'ils provoquent.^{26,27} Dans cette étude nous faisons l'hypothèse qu'une étude plus approfondie de l'asynchronisme électrique cardiaque par cartographie non invasive électrocardiographique (ECM) permettra une meilleure discrimination des potentiels répondeurs à la stimulation BIV. Trente-trois patients implantés d'un défibrillateur de resynchronisation ont été au préalable cartographiés en rythme spontané dans le but de : 1/décrire l'activation ventriculaire et 2/quantifier l'asynchronisme électrique par le biais des paramètres LVTAT, RVTAT et VEU (voir matériels et méthodes). Le pouvoir prédictif de réponse clinique à six mois (NYHA, absence d'hospitalisation ou décès) a été ensuite calculé pour ces paramètres d'asynchronisme ainsi que pour la durée du QRS et l'aspect de BBG.

8.2 RÉSULTATS:

8.2.1 Activation

Nous avons pu identifier des caractéristiques communes à l'activation ventriculaire des 18 patients présentant un BBG : activation VD rapide à partir de la primo activation VD, absence de primo activation VG, activation du VG à partir du VD selon deux fronts parallèles au grand axe cardiaque (un antérieur, un inférieur), présence d'une à quatre lignes de conduction lente orientées de la base vers l'apex (antéroseptale, antérolatérale, inféroseptale ou inférolatérale), fin de l'activation en région basolatérale.

Les schémas d'activation des 15 patients présentant un trouble de conduction aspécifique (NICD) sont apparus beaucoup plus hétérogènes : présence possible de primoactivations VG, lignes de conceptions lentes aléatoires moins nombreuses et plus courtes que dans le BBG, fin d'activation variable. En conséquence ces patients présentaient un LVTAT ($91\pm 34\text{ms}$ vs $115\pm 21\text{ms}$ BBG, $p=0.03$) et un VEU ($40\pm 22\text{ms}$ vs $75\pm 12\text{ms}$ BBG, $p<0.001$) significativement inférieur aux patients présentant un BBG.

8.2.2 Asynchronisme électrique et réponse

Vingt et un patients furent classés répondeur à 6 mois. En analyse ROC, l'aire sous la courbe pour la prédiction d'une réponse clinique à 6 mois était pour le VEU (0.88 [écart interquartiles 0.65-0.96]) significativement supérieure à celle obtenue pour la durée du QRS (0.73 [0.48-0.87] ; $p<0.05$ vs VEU) ou LVTAT (0.72 [0.48-0.87], $p=0.03$ vs VEU). Au seuil de 50ms, le VEU était prédictif d'une réponse clinique à six mois avec une sensibilité, spécificité, valeur prédictive positive et valeur prédictive négative de respectivement : 90%, 82%, 90% et 82%. Au même seuil la probabilité de réponse était multipliée par 42 en analyse univariée (OR 42.8 IC 95% [5.2 – 354.1], $p<0.001$). En comparaison l'odds ratio pour la présence d'un BBG était de 14.4 (IC 95% [2.3 – 89.9], $p=0.004$). Tous les patients avec BBG avaient un VEU>50ms et trois patients avec NICD (20%) présentaient également un VEU>50ms, ces trois patients furent cliniquement répondeurs.

Nous avons pour la première fois systématiquement décrit et comparé l'activation ventriculaire épicaudique des patients présentant un BBG ou un trouble de conduction aspécifique (NICD). Nous avons démontré malgré un effectif de patients réduit qu'une analyse détaillée de l'asynchronisme cardiaque permettait de prédire, mieux que l'ECG de surface, la réponse clinique à la stimulation biventriculaire. En particulier, le « découplage » d'activation du VG par rapport au VD (VEU) semble être une caractéristique essentielle du substrat éligible à la CRT. Ces résultats méritent d'être confirmés à plus grande échelle dans une étude multicentrique.

Noninvasive Electrocardiographic Mapping to Improve Patient Selection for Cardiac Resynchronization Therapy

Beyond QRS Duration and Left Bundle Branch Block Morphology

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Objectives	This study sought to investigate whether noninvasive electrocardiographic activation mapping is a useful method for predicting response to cardiac resynchronization therapy (CRT).
Background	One third of the patients appear not to respond to CRT when they are selected according to QRS duration.
Methods	We performed electrocardiographic activation mapping in 33 consecutive CRT candidates (QRS duration ≥ 120 ms). In 18 patients, the 12-lead electrocardiographic morphology was left bundle branch block (LBBB), and in 15, it was nonspecific intraventricular conduction disturbance (NICD). Three indexes of electrical dyssynchrony were derived from intrinsic maps: right and left ventricular total activation times and ventricular electrical uncoupling (VEU) (difference between the left ventricular [LV] and right ventricular mean activation times). We assessed the ability of these parameters to predict response, measured using a clinical composite score, after 6 months of CRT.
Results	Electrocardiographic maps revealed homogeneous patterns of activation and consistently greater VEU and LV total activation time (LVTAT) in patients with LBBB compared with heterogeneous activation sequences and shorter VEU and LVTAT in NICD patients (VEU: 75 ± 12 ms vs. 40 ± 22 ms; $p < 0.001$; LVTAT: 115 ± 21 ms vs. 91 ± 34 ms; $p = 0.03$). LBBB and NICD patients had similar right ventricular total activation times (62 ± 30 ms vs. 58 ± 26 ms; $p = 0.7$). The area under the receiver-operating characteristic curve indicated that VEU (area under the curve [AUC]: 0.88) was significantly superior to QRS duration (AUC: 0.73) and LVTAT (AUC: 0.72) for predicting CRT response ($p < 0.05$). With a 50-ms cutoff value, VEU identified CRT responders with 90% sensitivity and 82% specificity whether LBBB was present or not.
Conclusions	Ventricular electrical uncoupling measured by electrocardiographic mapping predicted clinical CRT response better than QRS duration or the presence of LBBB. (J Am Coll Cardiol 2013;61:2435–43) © 2013 by the American College of Cardiology Foundation

When 12-lead electrocardiography (ECG) is used to identify electrical dyssynchrony, approximately one third of the patients undergoing cardiac resynchronization therapy (CRT)

See page 2444

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la Recherche au titre du programme Investissements d'Avenir (ANR-10-IAHU-04). Drs. Strom and Ramanathan are paid employees and stockholders of CardioInsight Technologies, Inc. Dr. Shah and Dr. Wilkoff are consultants for CardioInsight Technologies, Inc. Dr. Hocini, Dr. Jaïs, and Dr. Haïssaguerre are stockholders of CardioInsight Technologies, Inc. Dr. Wilkoff is on the advisory boards of and has received honoraria from Medtronic, St. Jude Medical, and Spectranetics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 24, 2012; revised manuscript received November 10, 2012, accepted January 8, 2013.

Abbreviations and Acronyms

AUC = area under the curve

CRT = cardiac resynchronization therapy

ECG = electrocardiography

ECM = electrocardiographic mapping

LBBS = left bundle branch block

LV = left ventricular

LVTAT = left ventricular total activation time

NICD = nonspecific intraventricular conduction disturbance

NYHA = New York Heart Association

ROC = receiver-operating characteristic

RV = right ventricular

RVTAT = right ventricular total activation time

VEU = ventricular electrical uncoupling

VEU_{SR} = ventricular electrical uncoupling square-root transformed

appear not to obtain a substantial clinical response. Numerous efforts have been made to reduce the rate of nonresponse by improving patient selection using different nonelectrical measures of mechanical dyssynchrony and ventricular scar. However, despite showing early promise, none have as yet proved to be superior to the 12-lead ECG when tested in prospective, randomized studies. As a result, the international guidelines for CRT implantation continue to recommend the use of the 12-lead ECG when assessing potential CRT candidates (1–4).

The advantage of 12-lead ECG over nonelectrical methods is that it allows an assessment of the electrical substrate; CRT is, after all, an electrical therapy. Recent findings suggest that the degree and pattern of conduction disease are important in determining response to CRT. Patients with a narrow or moderately prolonged QRS duration do not appear to experience decreases in adverse

clinical events when treated with CRT (5,6). Patients with left bundle branch block (LBBS) are likely to respond, while those with right bundle-branch block or nonspecific intraventricular conduction disturbance (NICD) are unlikely to respond (7,8).

A disadvantage of 12-lead ECG is that it provides only a general overview of ventricular electrical activation abnormalities. In this study, we hypothesized that by making a more detailed assessment of electrical activation, it is possible to predict response to CRT more reliably than by using 12-lead ECG.

Electrocardiographic mapping (ECM) is a noninvasive mapping technique developed to provide detailed patient-specific information on epicardial electrical activation (9). Using this high-resolution mapping technique, we sought to: 1) characterize the ventricular activation sequence of patients with 12-lead ECG morphology of LBBS and compare it with the activation sequence observed in patients with prolonged QRS duration but without typical LBBS morphology (NICD group); and 2) explore the ability of different ECM-derived parameters of electrical dyssynchrony to predict long-term clinical response to CRT.

Methods

The execution of the study conformed to the principles outlined in the Declaration of Helsinki on research in human subjects. All patients gave written approval to

participate in the study, which was approved by the institutional ethics committee.

Patient population. The study population consisted of a cohort of 33 consecutive patients scheduled for CRT-device implantation based on the following criteria: 1) New York Heart Association (NYHA) functional class II, III, or IV despite optimal medical therapy; 2) left ventricular (LV) ejection fraction $\leq 35\%$ during sinus rhythm; and 3) intrinsic QRS duration ≥ 120 ms on 12-lead ECG. Heart failure etiology was considered ischemic in the presence of significant coronary artery disease ($\geq 50\%$ stenosis in ≥ 1 of the major epicardial coronary arteries) and/or a history of myocardial infarction or revascularization.

The mean age was 65 ± 9 years; 28 patients (85%) were male, 14 (42%) had an ischemic cardiomyopathy, 7 (21%) were NYHA functional class II, 25 (76%) were functional class III, and 1 (3%) was functional class IV. Mean LV ejection fraction was $27 \pm 4\%$, and QRS duration as derived from 12-lead surface ECG was 152 ± 22 ms. Intraventricular conduction disturbances were defined according to the most recent American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society criteria (10). Patients with right bundle branch block were excluded.

Device implantation and follow-up. All patients underwent implantation of a CRT defibrillator. Although the right ventricular (RV) lead was systematically implanted at the RV apex, the position of the LV lead was not pre-specified. The final position was determined by coronary venous anatomy with good stability, an acceptable pacing threshold, and no phrenic nerve capture.

All patients were clinically assessed by physicians who were blinded to the ECM data. The clinical assessment included estimation of NYHA functional class and acquisition of a 12-lead electrocardiogram (10 mm/mV; 25 mm/s) at 3 time points (i.e., before implantation and 3 and 6 months after implantation of their CRT device). Heart failure medications were adjusted as required, and adverse events (hospitalization or death) were recorded.

To assess CRT response, we used a clinical composite score that combined changes in clinical status (NYHA functional class) with the occurrence of major clinical events (hospitalization or death) (11). This score was previously used in studies evaluating the efficacy of CRT (12,13). Patients were considered as clinical responders if, during 6 months of follow-up, they remained alive, did not experience hospitalization for heart failure, and demonstrated an improvement of at least 1 NYHA functional class.

Noninvasive mapping of electrical activation. Ventricular epicardial activation maps were acquired during intrinsic sinus rhythm using a noninvasive, high-resolution ECM system (ECVUE, CardioInsight Technologies Inc., Cleveland, Ohio). As previously described in detail, body surface potentials were recorded from 252 sites around the entire surface of the torso (14). A thoracic computed tomography scan was performed with the electrodes attached to the

patient. The body surface potentials and computed tomography images were then combined and processed to reconstruct 1,500 epicardial unipolar electrograms. Ventricular activation times were calculated from the onset of the QRS duration to the maximal negative slope of each unipolar electrogram. An epicardial breakthrough site was defined as the earliest location identified on the isochrone map. A line of slow conduction was recorded if the activation times of adjacent points on either side of this line differed by >50 ms.

The following electrical dyssynchrony indexes were derived from intrinsic activation maps: the RV total activation time (RVTAT), defined as the duration (in milliseconds) from the earliest to the latest site of RV activation during intrinsic rhythm; the LV total activation time (LVTAT), defined as the duration (in milliseconds) from the earliest to the latest site of left ventricular activation during intrinsic rhythm; and ventricular electrical uncoupling (VEU), defined as the difference between the mean LV and RV activation times during spontaneous rhythm (in milliseconds). A positive value reflects LV uncoupling (from the right ventricle), whereas a negative value reflects RV uncoupling (from the left ventricle).

We tested whether these ECM-derived parameters were associated with clinical response to CRT. In addition, we investigated how these parameters related to the LBBB morphology and the QRS duration derived from 12-lead surface ECG. To test reproducibility of the electrical dyssynchrony indexes, the activation maps of 13 randomly selected patients were analyzed by 2 operators who were blinded to patient characteristics and outcome.

Statistical analysis. Categorical variables were expressed as absolute numbers (percentages) and compared using the chi-square test or the Fisher exact test, as appropriate. Continuous variables were expressed as mean \pm SD or median (interquartile range) and tested for normality using skewness, kurtosis, and omnibus tests. They were compared using either the Student *t* test or the Mann-Whitney *U* test, as appropriate. Interobserver variability of LVTAT, RVTAT, and VEU was assessed by an intraclass correlation coefficient. Receiver-operating characteristic (ROC) curves were generated, and areas under the curve (AUCs) were reported as a measure of the ability to predict a positive response. VEU was square-root transformed (VEU_{SR}) before the analysis. ROC AUCs were compared using the *z* test. For the purpose of comparison of categorical and continuous data, all significant continuous parameters were binarized using the best cutoff (greatest sum of sensitivity and specificity) found at ROC analysis. Then, binary logistic regression analyses giving odds ratios and 95% confidence intervals were used to explore the associations between electrical dyssynchrony parameters at baseline and positive response to CRT. Statistical analyses were performed using SPSS software, version 18.0 (SPSS Inc., Chicago, Illinois) and the NCSS software 2007 (NCSS

LLC, Kaysville, Utah). Statistical significance was assumed at *p* < 0.05.

Results

Electrical properties. Based on 12-lead ECG, 18 patients had an LBBB and 15 had an NICD. Compared with the NICD group, LBBB patients had a longer QRS duration (164 ± 16 ms vs. 137 ± 20 ms; *p* < 0.001), a longer LVTAT (115 ± 21 ms vs. 91 ± 34 ms; *p* < 0.03), and greater VEU (75 ± 12 ms vs. 40 ± 22 ms; *p* < 0.001). There were no significant differences between the 2 groups in terms of sex (males: 14 [78%] vs. 14 [93%]; *p* = 0.3), age (68 ± 9 years vs. 63 ± 9 years; *p* = 0.1), LV ejection fraction ($26 \pm 4\%$ vs. $27 \pm 5\%$; *p* = 0.7), or the presence of ischemic cardiomyopathy (6 [33%] vs. 8 [53%]; *p* = 0.3). Intraclass correlation coefficients were 0.92, 0.97, and 0.99 for LVTAT, RVTAT, and VEU, respectively. Baseline electrical characteristics of the 2 groups are summarized in Table 1.

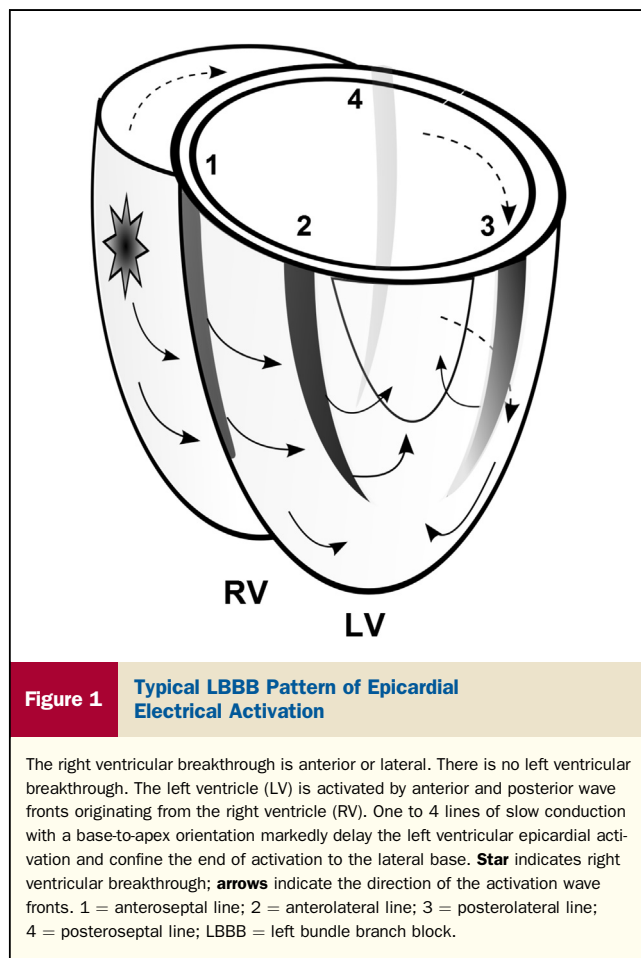
Electrocardiographic activation maps in 18 LBBB patients. All LBBB patients had a single anterior (11 [61%]) or lateral (7 [39%]) RV breakthrough site. Epicardial breakthrough was apparent 24 ± 8 ms after the QRS onset. RV epicardial activation propagated centrifugally from the breakthrough site to activate the entire RV epicardium within 61 ± 28 ms (Figs. 1 and 2). The base was the latest RV segment to be activated in 13 patients (72%). There was no epicardial breakthrough in the left ventricle, which was activated passively from the right ventricle via the septum (Figs. 1 and 2). The spread of the activation front was consistently impaired (both anteriorly and posteriorly) by lines of slow conduction (crowded isochrones). These lines were typically oriented in a base-to-apex direction and appeared on the anteroseptal, anterolateral, posterolateral, and posteroseptal surfaces. These lines of slow conduction usually extended for more than two thirds of the distance from base to apex and were multiple (median: 2 [interquartile range: 2 to 3]). They were responsible for the observed prolonged LVTAT and VEU. The latest site of LV activation was basolateral for the majority of patients (16 [89%]). We observed no association between the etiology of ventricular impairment and RVTAT (52 ± 18 ms vs. 67 ± 34 ms ischemic vs.

Table 1 Baseline Electrical Characteristics of the Patients by QRS Morphology

Parameter	LBBB (n = 18)	NICD (n = 15)	p Value
QRS duration, ms	164 ± 16	137 ± 20	<0.001
RVTAT, ms	62 ± 30	58 ± 26	0.7
LVTAT, ms	115 ± 21	91 ± 34	0.03
VEU, ms	75 ± 12	40 ± 22	<0.001

Values are mean \pm SD. QRS duration was measured with 12-lead electrocardiography. RVTAT, LVTAT, and VEU were calculated using the epicardial activation maps.

LBBB = left bundle branch block; NICD = nonspecific intraventricular conduction disturbance; RVTAT = right ventricular total activation time; LVTAT = left ventricular total activation time; VEU = ventricular electrical uncoupling.



nonischemic group; $p = 0.2$), LVTAT (114 ± 20 ms vs. 113 ± 26 ms; $p = 0.9$), VEU time (73 ± 16 ms vs. 76 ± 10 ms; $p = 0.6$), or the number of lines of slow conduction.

Electrocardiographic activation maps in 15 patients with nonspecific intraventricular conduction disturbance. Most (11 [73%]) of the NICD patients had a single RV breakthrough site, whereas 4 had additional sites of breakthrough in the left ventricle. In contrast to the LBBB group, activation sequences were heterogeneous among NICD patients. Breakthrough occurred a mean 27 ± 12 ms after QRS onset ($p = 0.4$ vs. LBBB). The RVTAT was similar to that measured in LBBB patients (58 ± 26 ms; $p = 0.9$ vs. LBBB), and the latest activated region of the right ventricle was usually basolateral. LV lines of slow conduction were present in 13 of the 15 patients. However, compared with the LBBB group, fewer lines of block were observed (median: 1 [interquartile range: 1 to 2]; $p = 0.002$ vs. LBBB), and when present, they were shorter (extending less than two thirds of the LV long axis) and their orientation was more variable (Figs. 3 and 4). As a consequence, LVTAT and VEU in NICD patients were shorter than in the LBBB group. Furthermore, we observed considerable variation in the location of the latest activated LV site: 4 anterobasal,

5 laterobasal, 3 posterobasal, 2 midlateral, and 1 apical. Ischemic patients displayed similar LVTATs (93 ± 39 ms vs. 89 ± 32 ms nonischemic group; $p = 0.8$) and VEU (45 ± 26 ms vs. 35 ± 18 ms nonischemic group; $p = 0.4$) compared with nonischemic patients. There was a trend toward higher RVTAT in the nonischemic group (48 ± 25 ms vs. 71 ± 24 ms nonischemic group; $p = 0.09$). The number of lines of slow conduction and the location of the latest activated area did not differ according to heart failure etiology.

Response to CRT. Of 33 patients, 21 (64%) met the clinical composite endpoint at 6 months and were identified as clinical responders. One patient experienced LV lead displacement after 3 months and was not further evaluated. During follow-up, 2 patients (6%) died and 3 (9%) were hospitalized due to worsening heart failure. The baseline characteristics of the responders and nonresponders are presented in Table 2. Responders had a longer baseline QRS duration (157 ± 19 ms vs. 139 ± 24 ms; $p < 0.05$), LVTAT (112 ± 29 ms vs. 89 ± 29 ms; $p < 0.04$), and VEU (72 ± 16 ms vs. 38 ± 23 ms; $p < 0.001$) than the nonresponders. LBBB was more prevalent in the responders compared with nonresponders (76% vs. 18%; $p = 0.003$).

Electrical parameters and prediction of response. In ROC analyses, QRS duration (AUC: 0.73 [interquartile range: 0.48 to 0.87]; $p = 0.034$), LVTAT (AUC: 0.72 [interquartile range: 0.48 to 0.87]; $p = 0.033$), and VEU_{SR} (AUC: 0.88 [interquartile range: 0.65 to 0.96]; $p = 0.004$) showed a significant AUC when tested for their ability to predict a positive CRT response. RVTAT was not useful in predicting response to CRT (AUC: 0.51 [interquartile range: 0.29 to 0.68]; $p = 0.45$). The AUC for VEU_{SR} was significantly higher than the AUC for QRS duration and LVTAT ($p = 0.045$ and $p = 0.031$, respectively), whereas AUC did not differ significantly between QRS duration and LVTAT ($p = 0.92$). The optimal cutoff value of VEU_{SR} to predict CRT response derived from the ROC analysis was 7.1 ms, which corresponded to a cutoff value of 50 ms for VEU. By using a cutoff level of 50 ms to define the presence of ventricular uncoupling, it was possible to predict response with sensitivity, specificity, and positive and negative predictive values of 90%, 82%, 90%, and 82%, respectively.

The best cutoff values for QRS duration, LVTAT, and VEU were determined using ROC analysis (145 ms, 101 ms, and 50 ms, respectively). These values were then used to binarize these parameters and run logistic regressions. Significant relationships obtained for these 3 binarized predictors and for native discrete parameters (LBBB morphology, sex, and ischemic etiology) are displayed in Table 3. VEU >50 ms was associated with a 42-fold increase in the likelihood of being a responder ($p < 0.001$).

In all LBBB patients ($n = 18$), VEU was >50 ms, whereas 3 NICD patients (20%) achieved this VEU cutoff. These 3 NICD patients were clinical responders.

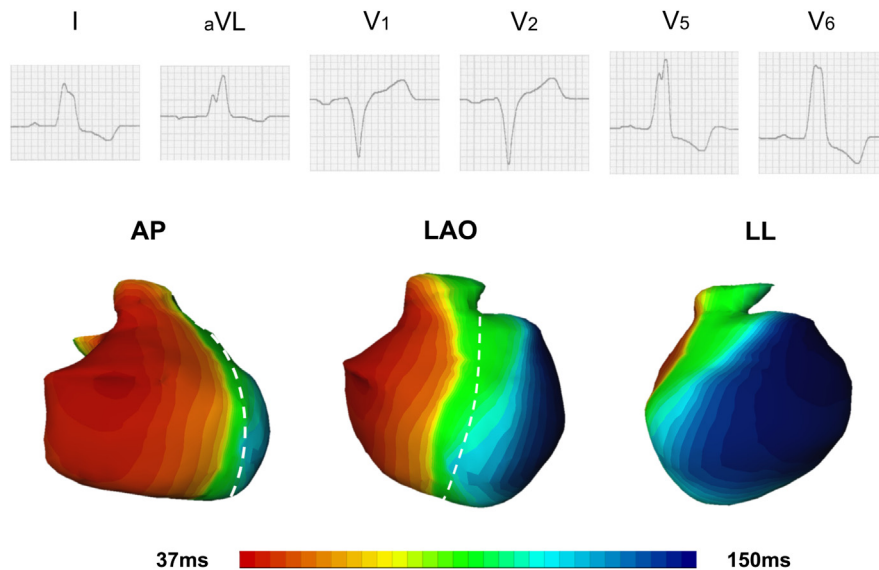


Figure 2 Electrocardiographic Activation Map of a Clinical Responder to CRT With a 12-Lead Surface ECG Exhibiting a Typical LBBB Activation Pattern

Epicardial ventricular surfaces of both ventricles are displayed in 3 views: anteroposterior (AP), left anterior oblique (LAO), and left lateral (LL). The left anterior descending artery is depicted as a **white dotted line**. The 12-lead electrocardiogram (ECG) shows a typical left bundle branch block (LBBB) morphology. The right ventricular lateral breakthrough is followed by a fast activation of this ventricle. The wave front spread to the left, with a first base-to-apex line of slow conduction at the level of the septum and a second one limited to the first two thirds of the anterolateral area (crowding of isochrones). Left ventricular activation ends at the lateral base. QRS duration: 155 ms; ventricular electrical uncoupling: 74 ms. CRT = cardiac resynchronization therapy.

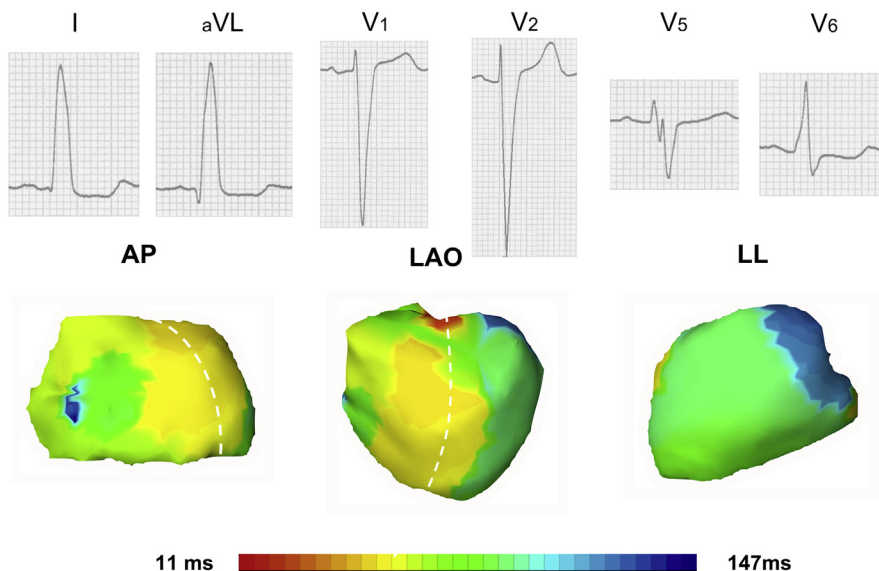
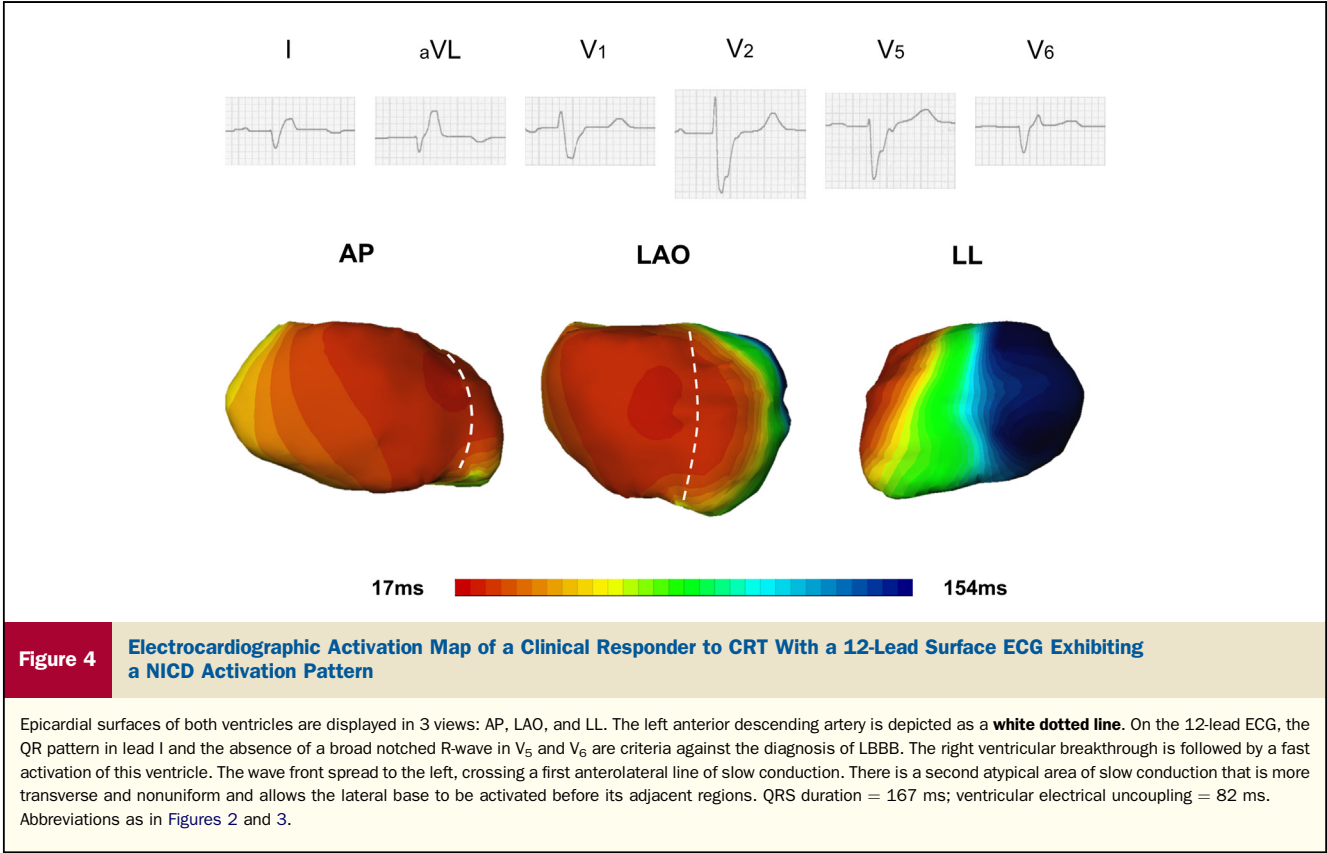


Figure 3 Electrocardiographic Activation Map of a Clinical Nonresponder to CRT With a 12-Lead Surface ECG Exhibiting a NICD Activation Pattern

Epicardial surfaces of both ventricles are displayed in 3 views: AP, LAO, and LL. The left anterior descending artery is depicted as a **white dotted line**. On the 12-lead ECG, the QR pattern in leads I and aVL and the absence of a broad notched R-wave in V₅ and V₆ are criteria against the diagnosis of LBBB. There is a septobasal breakthrough with an eccentric activation followed by a heterogeneous and abnormally slow activation of the RV with delayed activated midlateral area. Left ventricular activation is slowed by an incomplete anterolateral line of slow conduction. The latest site of activation is the lateral base. QRS duration: 166 ms; ventricular electrical uncoupling: 35 ms. NICD = nonspecific intraventricular conduction disturbance; other abbreviations as in Figures 1 and 2.



Discussion

In this study, we show that noninvasive 3-dimensional activation mapping is useful in predicting which patients will respond to CRT. Prolongation of VEU was strongly associated with clinical CRT response and appeared to be a more powerful predictor than 12-lead ECG parameters. Such mapping also showed relatively consistent patterns of activation in patients with LBBB and pronounced VEU. In contrast, prolonged QRS duration without typical bundle branch block morphology (NICD) appears to represent a heterogeneous group of

conduction defects. In the majority of cases, these defects do not appear amenable to treatment with conventional CRT. However, ECM identified pronounced prolongation of VEU in a subset of patients with NICD (20%), and these patients did appear to experience a clinical response after CRT.

LBBB versus NICD electrocardiographic activation maps. LEFT BUNDLE BRANCH BLOCK. Detailed analysis of the ventricular activation pattern in patients with LBBB on 12-lead ECG revealed the following major features: 1) RV breakthrough gave rise to a rapid and centrifugal spread of activation across the RV free wall; 2) there was no LV breakthrough; 3) 1 to 4 LV lines of slow conduction oriented in base-to-apex direction prevented rapid LV conduction; and 4) the site of latest activation occurred usually at the base of the lateral wall of the left ventricle.

Table 2 Baseline Characteristics of Responders and Nonresponders to CRT			
Baseline Characteristics	Responders (n = 21)	Nonresponders (n = 11)	p Value
Age, yrs	65 ± 8	67 ± 11	0.5
Male	17 (81)	11 (100)	0.3
Ischemic cardiomyopathy	8 (38)	6 (55)	0.5
Ejection fraction	26 ± 4	26 ± 4	0.9
QRS duration, ms	157 ± 19	139 ± 24	<0.05
LBBB pattern	16 (76)	2 (18)	0.003
RVTAT, ms	60 ± 30	59 ± 25	0.9
LVTAT, ms	112 ± 29	89 ± 29	0.04
VEU, ms	72 ± 16	38 ± 23	<0.001

Values are mean ± SD or number (%) of observations. QRS duration was measured with 12-lead echocardiography. RVTAT, LVTAT, and VEU were calculated using the epicardial activation maps. CRT = cardiac resynchronization therapy; other abbreviations as in Table 1.

Table 3 Association Between Electrical Parameters and CRT Response: Univariate Analysis		
Parameter	OR (95% CI)	p Value
QRS duration, ms*	7.4 (1.4–38.4)	0.017
LBBB	14.4 (2.3–89.9)	0.004
LVTAT†	5.3 (1.1–26.6)	0.04
VEU‡	42.8 (5.2–354.1)	<0.001

Right ventricular total activation time, LVTAT, and VEU were calculated using the epicardial activation maps. QRS duration was measured with 12-lead electrocardiography. *QRS duration using a 145-ms cutoff. †Using a 101-ms cutoff. ‡Using a 50-ms cutoff. OR = odds ratio; CI = confidence interval; other abbreviations as in Tables 1 and 2.

Relatively few human data are available with regard to the epicardial activation sequence in patients with LBBB. Wyndham et al. (15) performed epicardial contact mapping (with a handheld probe) in 5 patients with LBBB during surgery. Using 54 to 70 acquisition points per patient, they described a normal RV activation sequence, the consistent absence of LV breakthrough, and the phenomenon of lines of slow conduction over the anterior and posterior septal regions. Jia et al. (14) used ECM in 6 patients with LBBB. They confirmed that the RV activation pattern was consistent with that observed in the normal heart and detected lines of slow conduction, mainly on the anterior LV surface.

In the present study, we provide a more systematic description of the lines of slow conduction, which vary in length and number but appear consistently at a few typical anatomic locations (Fig. 1). We found these lines to be more prominent at the base, which may account for the finding that the basal region is typically the latest area to be activated.

NICD. In contrast, NICD patients demonstrated heterogeneous patterns of activation: 1) breakthrough could also occur on the LV surface; 2) lines of slow conduction were fewer (or even absent) and smaller and varied in geometric location; 3) the site of latest activation was highly variable. To the best of our knowledge, we present the first human data on the epicardial activation sequences in patients with NICD. In contrast to patients with LBBB displaying a “typical” activation pattern, the activation sequences in NICD are highly variable. Therefore, this group of patients particularly benefited from the innovative ECM assessment of the underlying electrical conduction abnormality.

Electrical dyssynchrony and CRT response. It is now accepted that sufficient ventricular electrical conduction delay needs to be present for CRT to produce improvements in cardiac pump function. Twelve-lead ECG is the most frequently used and best validated technique for measuring this conduction delay. No reduction in heart failure events post-CRT was observed in patients with a QRS duration <150 ms in a subgroup analysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy) trial (16). This finding was confirmed in a meta-analysis of 5 randomized, controlled trials that included >5,800 patients (6). The pattern of conduction disturbance also appears to be critical in determining a response to CRT. A further subgroup analysis of the MADIT-CRT trial showed that only patients with LBBB derived substantial clinical benefit from CRT (7). Again, this result was subsequently supported by the results of a meta-analysis (8). As a result of these findings, the 2012 European Society of Cardiology guidelines for the management of heart failure have been revised to recommend CRT only in the patients with LBBB (Class I, Level of Evidence: A) or a QRS duration \geq 150 ms (Class IIa, Level of Evidence: A) (4). In patients with NYHA functional class I or II heart failure, the U.S. Food and Drug

Administration allows CRT only in patients who are in sinus rhythm with LBBB (17). These guideline modifications have been made in response to the reports of high rates of nonresponders to CRT. They are aimed at improving the specificity of the selection process, but inevitably result in a reduced sensitivity. As a result, CRT device implantation is currently discouraged in patients with NICD with a QRS duration <150 ms. However, there is evidence that a proportion of patients with NICD respond to treatment with CRT (18,19). In the aforementioned meta-analysis, the authors acknowledged that the neutral effect of CRT in patients with moderately prolonged QRS duration may be actually due to a subset of patients at increased risk of hospitalizations and death. The same assumption may apply to the NICD patients, as evidenced by the high prevalence of ischemic cardiomyopathy in this group, a factor known to adversely affect the prognosis (4,18,19). Given the high proportion of patients presenting with NICD (approximately one third of the recent RAFT [Resynchronization–Defibrillation for Ambulatory Heart Failure Trial] and REVERSE [Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction] trials) and/or QRS duration <150 ms (40% of the European CRT survey) as well as the demonstrated clinical and survival benefits of CRT, additional selection criteria are clearly needed for identifying potential responders (13,20,21).

Studies investigating the electrical substrate beyond QRS duration or LBBB morphology are scarce. Sweeney et al. (22) carefully inspected standard 12-lead electrocardiograms of patients with LBBB who received CRT. The LVTAT was measured between a notch occurring 40 ms after the QRS onset (which was assumed to be the RV-LV transition) and the end of the QRS complex. Increasing LVTAT was associated with a greater probability of remodeling up to a plateau value of 125 ms. This estimate of LVTAT, however, is only applicable to some LBBB patients who exhibit a clear notch in the QRS complex. The LVTAT has also been estimated invasively by calculating the delay between QRS onset and LV activation measured from the LV lead. Varma (23) observed that this LV electrical delay exceeded 100 ms in 87% of LBBB patients compared with only 45% in those with RBBB. Singh et al. (24) corrected this delay for QRS duration and found that patients with a reduced baseline LV lead electrical delay (<50% of the QRS duration) had a worse clinical outcome at 12 months. Clearly, this parameter is dependent on LV lead position, which is not necessarily positioned in the latest activated region. Using LV noncontact endocardial mapping, Fung et al. (25) observed that patients with lines of slow conduction had a more favorable response to CRT than those without these lines. Auricchio et al. (26) first reported that 23 of 24 LBBB patients (96%) showed LV lines of slow conduction. Besides confirming the presence of these lines in patients with LBBB, we also found that the prevalence of lines of slow conduction was significantly lower in NICD patients.

The latter finding may explain why the presence of lines of slow conduction has previously been found to be associated with CRT response (25).

In the present study, we measured RVTAT as well as LVTAT by using >1,000 reconstructed electrograms. This allowed us to clearly define the area of latest activation. We observed that VEU was a stronger predictor of CRT response than LVTAT. In our study, LVTAT was not superior to QRS duration for predicting clinical response. Our finding that VEU >50 ms is predictive of a positive CRT response suggests that electrical uncoupling of the left ventricle from the right ventricle is a fundamental component of the electrical substrate, which is amenable to treatment with CRT. VEU can be prolonged by 2 main mechanisms. First, because of a delay in the onset of LV activation relative to RV activation, this is determined mainly by the transseptal activation time. Second, because of an intraventricular-conduction delay, slowing of LV conduction by lines of slow conduction increases VEU, whereas slowing of RV activation can mitigate it. It is likely that a delay in LV activation relative to RV activation is responsible for dynamic alterations in transseptal pressure differences and presystolic shortening of septal muscle fibers, both resulting in a loss of septal contribution to the LV ejection fraction. Preserved RV activation also appears to be important. The presence of an RV conduction delay reduces VEU. This finding may explain why RV dysfunction has been negatively associated with CRT response (27). LV electrical uncoupling was found in all LBBB patients, which may account for the high rate of response to CRT in this subgroup. Interestingly, LV electrical uncoupling was also observed in some patients with NICD and appeared to be useful in identifying responders to CRT in this group.

VEU, therefore, has the potential to be a useful measure for selecting patients who may benefit from CRT, particularly patients who have prolonged QRS duration on surface ECG, but who do not display typical LBBB morphology.

Study limitations. The number of patients included in this study is modest; however, this is the largest study to date of detailed mapping of electrical activation abnormalities in patients undergoing CRT. Larger, randomized, and blinded studies are required to confirm these results. Patient selection is undoubtedly a major issue for CRT response. Optimization of the therapy delivery is also of major importance. In this regard, lead placement under real-time ECM assistance would be an interesting field of investigation.

Conclusions

Patients with LBBB have uniform patterns of activation when measured using detailed electrocardiographic maps, whereas in patients with NICD, conduction patterns are highly variable. This noninvasive 3-dimensional mapping tool derives a novel electrical dyssynchrony parameter called VEU, which is significantly associated with a clinical

response to CRT. VEU, which is consistently elevated in all LBBB but in only a few NICD patients, properly identifies clinical CRT responders in both of these subgroups. Thus, with substantial advantage over standard 12-lead ECG in identifying clinical responders to CRT, ECM can potentially improve prospective decision-making on candidacy for CRT.

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Key Words: cardiac resynchronization therapy ■ electrocardiography ■ electrical dyssynchrony ■ heart failure ■ ventricular mapping.

9 ANALYSE PAR CARTOGRAPHIE ELECTROCARDIOGRAPHIQUE DE L'ACTIVATION INDUITE PAR LA STIMULATION APICALE VENTRICULAIRE DROITE ET DE L'ACTIVATION DE BLOC DE BRANCHE GAUCHE : COMPARAISON ET IMPLICATION POUR LA THERAPIE DE RESYNCHRONISATION CARDIAQUE.*

* Eschalier R, Ploux S, Lumens J, Whinnett Z, Varma N, Meillet V, Ritter P, Jaïs P, Haïssaguerre M, Bordachar P. Detailed Analysis of Ventricular Activation Sequences during Right Ventricular Apical Pacing and Left Bundle Branch Block, and the Potential Implications for Cardiac Resynchronization Therapy. Heart Rhythm. 2014 Oct 3.

9.1 INTRODUCTION

La stimulation ventriculaire droite va entrainer de facto un retard d'activation du VG par rapport au VD avec un élargissement du QRS. En outre, la stimulation VD est considérée par certains comme un modèle acquis de BBG.⁶⁰ La stimulation BIV a donc été proposée en remplacement d'une stimulation VD unique pour les patients insuffisants cardiaques à FE<35%. Cette stratégie dite d' « up-grading », est actuellement recommandée en l'absence de larges essais randomisés ayant évalué son efficacité (recommandation de classe I, niveau B).⁶¹ Cependant, toutes les études ne sont pas favorables à une telle attitude : dans l'essai randomisé RAFT ayant évalué l'efficacité de la resynchronisation chez des insuffisants cardiaques en stade II et III de la NYHA avec QRS>120ms ou >200ms en cas de stimulation VD, le groupe des patients stimulés sur le VD (n=135) ne tirait pas bénéfice de la CRT.⁶² Dans cette étude, nous nous proposons d'évaluer l'asynchronisme cardiaque par technique de cartographie électrocardiographique dans un groupe de patient présentant un BBG (n=24), en condition d'activation spontanée, de stimulation VD et BIV.

9.2 RESULTATS

En configuration d'activation spontanée (BBG), le VD était rapidement activé à partir d'une unique primo activation ventriculaire droite. Durant la stimulation VD, le VD était activé à partir

de l'apex, initiant un front d'activation excentrique. Ce front d'activation va ralentir sa conduction pour former un périmètre de conduction lente, au-delà duquel la conduction apparaissait plus uniforme. Il en résulte un prolongement significatif du temps d'activation VD (RVTAT). La stimulation BIV va de même prolonger le temps d'activation VD, sans que l'activation soit forcément similaire (en partie en raison de la présence de ligne de conduction lentes induites par la stimulation VG).

Au niveau du VG, les temps d'activation étaient similaires pour l'activation spontanée et la stimulation VD, avec une fin d'activation en région basolatérale dans les deux cas. En revanche le schéma d'activation différait entre les deux configurations. Avec une activation circonferentielle selon deux fronts ralentis au niveau de lignes basoapicales de conduction lente pour l'activation de BBG ; contre une activation apicobasale du VG, avec présence de lignes de conduction lente basoapicales (plus courtes) mais aussi transversales en cas de stimulation VD.

Si le temps total d'activation VG (LVTAT) était similaire dans les deux configurations (117 ± 29 vs 103 ± 22 ms pour BBG, $p=0.06$), le VEU différait significativement: 38 ± 21 vs 73 ± 12 ms pour BBG, $p<0.001$. Ainsi le retard d'activation VG par rapport au VD était beaucoup plus important durant activation spontanée de BBG que pendant la stimulation VD.

Dans cette étude, nous avons pu comparer l'activation du BBG à la stimulation apicale VD, à substrat anatomique constant (mesures répétées sur un même patient). D'importantes différences ont été mises en évidence, en particulier au niveau de l'activation VD. Ces différences se traduisent en termes d'asynchronisme « interventriculaire » avec un VEU diminué par la stimulation apicale VD par rapport au BBG. Nous avons précédemment démontré que le VEU est une composante fondamentale du substrat électrique optimal pour la CRT notamment au-delà de 50ms. Dans l'étude de Leclercq et co. la stimulation biventriculaire apparaissait bénéfique sur une population de patients chroniquement stimulés sur le VD mais sélectionnés sur la base d'un asynchronisme interventriculaire échocardiographie (délai prééjectionnel interventriculaire >40 ms).⁶³ En conclusion, toute stimulation VD apicale n'est pas aussi délétère que l'activation de BBG en termes d'asynchronisme; nous préconisons une étude individuelle de l'asynchronisme électrique en prévision d'une éventuelle procédure d'upgrade.

Detailed Analysis of Ventricular Activation Sequences during Right Ventricular Apical Pacing and Left Bundle Branch Block, and the Potential Implications for Cardiac Resynchronization Therapy

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www.elsevier.com/locate/buildenv

PII: S1547-5271(14)01123-0
DOI: <http://dx.doi.org/10.1016/j.hrthm.2014.09.059>
Reference: HRTM5952

To appear in: *Heart Rhythm*

Cite this article as: Romain Eschalier MD, PhD, Sylvain Ploux MD, Joost Lumens PhD, Zachary Whinnett MD, PhD, Niraj Varma MD, Valentin Meillet MSc, Philippe Ritter MD, Pierre Jaïs MD, Michel Haïssaguerre MD, Pierre Bordachar MD, PhD., Detailed Analysis of Ventricular Activation Sequences during Right Ventricular Apical Pacing and Left Bundle Branch Block, and the Potential Implications for Cardiac Resynchronization Therapy, *Heart Rhythm*, <http://dx.doi.org/10.1016/j.hrthm.2014.09.059>

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**DETAILED ANALYSIS OF VENTRICULAR ACTIVATION SEQUENCES DURING RIGHT
VENTRICULAR APICAL PACING AND LEFT BUNDLE BRANCH BLOCK, AND THE POTENTIAL
IMPLICATIONS FOR CARDIAC RESYNCHRONIZATION THERAPY**

Brief Title: Comparison between RV pacing and LBBB activations.

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Conflicts of Interest : Dr. Lumens has received a grant in the framework of the Dr. E. Dekker program of the Dutch Heart Foundation (NHS-2012T010). Dr Whinnett is supported by the British Heart Foundation (FS/13/44/30291). This work was supported by the French Government : l'Agence National de la Recherche au titre du programme Investissements d'Avenir (ANR-10-IAHU-04). Pr. Jaïs, and Pr. Haïssaguerre are stockholders of CardioInsight Technologies, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Sources of financial support: None

Total word count: 4381

ABSTRACT

Background. Left Bundle Branch Block (LBBB) leads to prolonged left ventricular (LV) total activation time (TAT) and ventricular electrical uncoupling (VEU: mean LV activation time minus mean right ventricular (RV) activation time); both have been shown to be preferential targets for cardiac resynchronization therapy (CRT). Whether RV apical pacing (RVAP) produces similar ventricular activation patterns has not been well studied.

Objective. To compare electrical ventricular activation patterns during RVAP and LBBB.

Methods. We performed electrocardiographic mapping (ECM) during sinus rhythm, RVAP and CRT in 24 patients with LBBB.

Results. We observed differences in the electrical activation pattern with RVAP compared to LBBB. During LBBB, RV activation occurred rapidly; in contrast RV activation was prolonged during RVAP (46 ± 21 vs. 69 ± 17 ms, $p < 0.001$).

There was no significant difference in LVTAT, however, differences in conduction pattern were observed. During LBBB LV activation was circumferential whereas with RVAP it proceeded from apex-to-base. Differences in the number, size and orientation of lines of slow conduction were also observed.

With LBBB, VEU was nearly twice as long as during RVAP (73 ± 12 vs. 38 ± 21 ms, $p < 0.001$). CRT resulted in a greater reduction in VEU relative to LBBB activation ($p < 0.001$).

Conclusion. RVAP produces significant differences in ventricular activation characteristics compared to LBBB. Significantly less VEU occurs with RVAP and as a result CRT produces a smaller relative reduction in VEU. This may explain the finding that CRT appears to be more effective in patients with LBBB than in patients upgraded because of high percentages of RV pacing.

Key words : Cardiac resynchronization therapy ; Electrocardiography ; Electrical dyssynchrony ; Ventricular mapping ; Left bundle-branch block.

LIST OF ABBREVIATIONS

BVP: Bi-ventricular pacing

CRT: Cardiac resynchronization therapy

HF (REF): Heart Failure (with reduced ejection fraction)

LBBB: Left bundle branch block

LV: Left ventricle

RV: Right ventricle

RVAP: Right ventricular apical pacing

TAT: Total activation time

VEU: Ventricular electrical uncoupling

INTRODUCTION

Several randomized control trials have found cardiac resynchronization therapy (CRT) to be beneficial in heart failure patients with reduced left ventricular ejection fraction and prolonged QRS duration¹⁻⁶. Sub-analysis of data from these trials suggests that patients with left bundle branch block (LBBB) are most likely to obtain benefit^{7,8}.

We have previously found that inter-ventricular dyssynchrony, measured by epicardial non-invasive electrocardiographic mapping, may be even better at predicting clinical CRT response, than QRS duration or the presence of LBBB⁹.

Right ventricular apical pacing (RVAP), like intrinsic activation with LBBB, is expected to result in delayed left ventricular activation. Patients who receive a high percentage of RVAP and have impaired left ventricular function have therefore been proposed as a group of patients who may also stand to gain from BVP. However, the results of small non-randomized studies which have assessed this strategy^{10,11}, have been contradictory. In the RAFT study¹², a minority of the included patients were previously chronically paced in the RV; sub analysis suggested that this group did not obtain benefit from the addition of an LV lead. No physiopathological mechanism has been proposed to explain this absence of benefit. Indeed, no detailed activation mapping has been previously performed to compare the respective electrical activation sequences during LBBB and RVAP.

The aims of the present study were; firstly, to systematically describe and compare qualitative and quantitative characteristics of ventricular electrical activation during LBBB and RVAP. In order to eliminate anatomic substrate as a variable, we made within patient comparisons. Secondly, we aimed to determine the impact BVP has on these activation characteristics.

METHODS

The execution of the study conformed to the principles outlined in the declaration of Helsinki on research in human subjects. All patients granted their written approval to participate in the study, which was approved by the local institutional ethics committee.

Patient population

The study population consisted of 24 patients with LBBB who were scheduled for CRT-device implantation based on the following criteria: New York Heart Association (NYHA) functional class II or III despite optimal medical therapy and left ventricular (LV) ejection fraction $\leq 35\%$ during intrinsic rhythm and typical LBBB activation on the 12 leads ECG according to the most recent AHA/ACCF/HRS criteria¹³.

Mean age was 70 ± 9 year's old, 18 (75 %) were male, 6 (25 %) had an ischemic cardiomyopathy (defined as a history of myocardial infarction or prior revascularization), 7 (29 %) patients were in NYHA Class II and 17 (71 %) in Class III. Mean LV echocardiographic ejection fraction was $26.5 \pm 5\%$ and mean baseline QRS duration measured from the 12-lead surface ECG was 162 ± 13 ms.

The 24 patients were implanted with a cardiac resynchronization therapy-defibrillator via a percutaneous transvenous approach. The RV lead was systematically positioned at the RV apex. The final LV lead position depended on the coronary venous anatomy, lead stability, pacing threshold and the need to avoid phrenic nerve stimulation. Within 72 hours of device implantation all patients had electrocardiographic mapping performed.

Noninvasive mapping of electrical activation

Ventricular epicardial activation maps were acquired using a noninvasive, high-resolution

electrocardiographic mapping system (ECVUE™, CardioInsight Technologies Inc, Cleveland, Ohio) during intrinsic rhythm (LBBB), right ventricular apical pacing (RVAP) and biventricular pacing (BVP) in VDD or DDD modes. During ventricular pacing the sensed/paced atrioventricular delay was programmed to the longest delay that resulted in complete ventricular capture. We used the 12 lead ECG to determine the onset of ventricular fusion which was defined as any changes in the width or morphology of the QRS.

As previously described in detail, body surface potentials were recorded from 252 sites around the entire surface of the torso¹⁴. A thoracic computed tomography scan was acquired with the electrodes attached to the patient. The body surface potentials and computed tomography images were then combined and processed to reconstruct 1500 epicardial unipolar electrograms. The different local ventricular activation times were calculated from the onset of the QRS or the pacing spike to the maximal negative slope of each unipolar electrogram. An epicardial breakthrough site was defined as the earliest location identified on the isochrones map. A line of slow conduction was recorded if the onset of activation of adjacent points differed by ≥ 50 ms (Figure 1). The following electrical dyssynchrony indexes were derived from intrinsic (LBBB) and paced (RVAP and BVP) activation maps using a point-by-point method: the RV total activation time (RVTAT), defined as the difference between the latest and earliest (in milliseconds) sites of RV activation; the LV total activation time (LVTAT), defined as the difference between the latest and earliest sites of left ventricular activation; and ventricular electrical uncoupling (VEU), defined as the difference (in milliseconds) between the mean LV and RV activation times.

Statistical analysis

We have presented categorical variables as absolute numbers (percentages) while continuous variable were expressed as mean (SD) or median (minimum - maximum). McNemar test was

used to compare the LV latest activated area, the number and length of lines of slow conduction between RVAP and LBBB. The dyssynchrony parameters (TAT, RVTAT, LVTAT and VEU) were compared among the different electrical activation patterns (LBBB, RVAP, BVP) by using repeated measures analysis of variance. Bonferroni correction was used for post hoc comparisons. Statistical analyses were performed using the SPSS software, version 18.0 (SPSS Inc., Chicago, IL). Statistical significance was assumed at $p < 0.05$.

RESULTS

Right ventricular electrical activation

We observed similarities but also major differences in terms of RV electrical activation during LBBB and RVAP. In both situations, there was only one RV breakthrough. During LBBB, we observed a single anterior [$n=17$ (71 %)] or lateral [$n=7$ (29 %)] RV breakthrough site. During RVAP, as expected, we always observed an apical RV breakthrough site. During LBBB, RV electrical activation was rapid and lines of slow conduction were not observed. In contrast with RVAP, right ventricular propagation appeared to occur more slowly with curvilinear lines of slow conduction observed around the pacing site. As a result right ventricular total activation time (RVTAT) was significantly longer during RVAP (69 ± 17 ms vs. 46 ± 21 ms, $p < 0.001$) (Table 1) compared to LBBB (Figures 2 and 3).

The RV base was always the latest activated RV free wall area during RVAP (100%), this was also the case in the majority of patients during intrinsic LBBB activation (19 patients, 79%, $p < 0.001$ vs. RVAP).

Biventricular pacing significantly changed RV electrical activation compared to LBBB, with prolongation of RVTAT being the most pronounced change (76 ± 15 ms vs. 46 ± 21 ms, $p < 0.001$). In contrast, no significant difference in RVTAT was observed between RVAP and

BVP, (69 ± 17 ms vs. 76 ± 15 ms during BVP, $p=0.30$). However, we did observe additional short RV lines of slow conduction at the RV base during BVP (Table 1).

Left ventricular electrical activation

We detected no significant difference in LVTAT with RVAP and LBBB though there did appear to be a trend for longer activation with RVAP (117 ± 29 ms vs. 103 ± 22 ms during LBBB, $p=0.06$) (Table 1).

There were also similarities with respect to ventricular activation pattern. Epicardial LV breakthrough was not observed with either LBBB or RVAP and the LV base was always the area of latest activation (Figure 1).

There were, however, also differences in LV activation pattern. The site of earliest LV activation was consistently localized at the apex during RVAP; this was followed by a single and circumferential activation front proceeding in an apex-to-base direction. In contrast, during intrinsic conduction with LBBB, the left ventricle was circumferentially invaded by two opposite fronts of activation: paraseptal anterior and posterior. During LBBB, we observed multiple [median: 2 (range: 1 to 4)] lines of slow conduction oriented in LV base-to-apex direction (activation delay occurred in a longitudinally direction). More than 70 % of the lines of slow conduction extended for more than half of the distance from the base to apex.

In contrast, during RVAP, fewer lines of slow conduction were observed [median: 1 (range: 0 to 2), $p=0.006$ vs. LBBB]. Also, these lines of slow conduction were typically shorter (55% extended for more than half of the distance from the apex to base) compared to the ones present during LBBB ($p=0.002$). The orientation was circumferential in 35% and apex-to-base in 65% of the cases (the activation was also transversally slowed down).

Biventricular pacing induced a complete change in the LV activation pattern: the initial activation spread from the LV pacing site (actual LV pacing site was patient specific as it was

dependent on anatomical factors). The number, orientation and shape of the lines of slow conduction differed compared to those observed during intrinsic LBBB activation and RVAP. They were predominantly localized around the LV pacing site. Left Ventricular TAT was significantly shorter during BVP compared to RVAP (97 ± 19 ms vs. 116 ± 27 ms; $p < 0.01$) but similar values were observed during LBBB (97 ± 19 ms vs. 103 ± 22 ms during LBBB; $p = 0.54$) (Table 1).

Ventricular electrical uncoupling

Ventricular electrical uncoupling (the difference between the mean LV and RV activation times) was less pronounced during RVAP than during LBBB (38 ± 21 vs. 73 ± 12 ms, $p < 0.001$). This is most likely due to the fact that RV activation was substantially prolonged during RVAP compared to intrinsic activation (LBBB). As a result, BVP produced a greater relative reduction in VEU when compared to LBBB rather than RVAP (-66 ± 31 ms vs. -31 ± 20 ms, $p < 0.001$) (Table 1).

DISCUSSION

In the present study, we observed significant differences in ventricular activation duration and patterns with RVAP compared to intrinsic activation with LBBB. Importantly comparisons were made within individual patients and therefore pacing site and myocardial structure remained constant. These findings may have important implications for the application of cardiac resynchronization therapy to patients with high percentages of RV pacing and LV impairment.

In large randomized trials, patients with LBBB obtained the greatest benefit from cardiac resynchronization therapy^{7,8}. Detailed ventricular activation mapping, suggests that the

mechanism for this improved response is that LBBB results in more pronounced ventricular uncoupling (i.e. larger LV activation time delay relative to the RV activation) than is observed with nonspecific intraventricular conduction disturbance⁹. A reduction in ventricular uncoupling appears to be the dominant mechanism through which BVP produces ventricular resynchronization.

Right ventricular apical pacing produces QRS prolongation, dyssynchronous ventricular activation and would therefore also be expected to result in important VEU. This assumption has led to the strategy of upgrading symptomatic heart failure patients, who receive high percentages of RV pacing, to biventricular pacing devices.^{10,15,16}

However despite encouraging results in some early small observational studies^{17–19} these were not subsequently replicated (on LV remodeling, NYHA class and quality of life)^{10,11}. Only small numbers of patients have been included in randomized studies, but in this study CRT was not found to reduce death or hospitalization for HF, in patients with chronic RV pacing¹².

Electrical activation differences between LBBB and RVAP

Our results provide a potential mechanistic explanation, for the unexpected finding of a lack of benefit with CRT in patients who have a history of chronic RV pacing. These results were consistent with some previously presented (Varma *et al.*, Heart Rhythm Society congress 2008). Electrical activation delays were confirmed by mechanical data. However, in the present study we measured times of activation and patterns during LBBB and RV pacing but also the impact of CRT.

1) Right ventricular pacing appears to result in very different right ventricular activation characteristics compared to those observed during intrinsic activation with LBBB. During

RVAP, right ventricular activation is slower and therefore less efficient than during LBBB. As a result, BVP produces less efficient RV activation compared to LBBB, but there appears to be no significant difference in RV activation with BVP compared with RV apical pacing only.

2) During right ventricular pacing, LV activation appears to be less efficient than during native conduction with LBBB (trend for prolonged LVTAT and different orientations of lines of slow conduction). Delivery of BVP therapy produces greater reductions in left ventricular activation times relative to RVAP than when it is compared with intrinsic conduction with LBBB.

3) The VEU, a parameter related to inter-ventricular dyssynchrony and probably a major determinant of response after CRT was during intrinsic LBBB activation nearly twice as high as that of the RVAP. Biventricular pacing produces larger reductions in inter-ventricular dyssynchrony relative to LBBB activation compared with those observed relative to RV apical pacing. This is because bi-ventricular pacing prolongs RV activation time in conjunction with a reduction in LV activation time, which has the net effect of reducing inter-ventricular dyssynchrony. Whereas when compared to RVAP, the main effect of BVP is to reduce only LVTAT, since RV activation occurs via the RV pacing lead in both cases. This produces a smaller reduction in ventricular electrical uncoupling.

The larger reduction in LV activation time with BVP relative to RV apical pacing, if considered in isolation would appear to favour biventricular pacing in RV pacing over native LBBB. However, when effects of BVP on both ventricles are considered we found a greater reduction in inter-ventricular dyssynchrony relative to native LBBB activation. We believe that a reduction in inter-ventricular dyssynchrony is the dominant resynchronization

mechanism through which BVP improves cardiac function. Therefore the observed greater efficiency of CRT in patients with LBBB may be explained by the larger reduction in VEU compared with RV apical pacing.

The importance of VEU is supported by our previous work, where we found the reduction in VEU to be an important predictor for CRT response⁹. In a population of 32 heart failure patients, a VEU above 50 ms was associated with a 42-fold increase in the likelihood of being a clinical responder at 6 months ($p < 0.001$). Moreover, VEU was found to be a better predictor for positive CRT response than QRS duration, LVTAT or a LBBB morphology. In light of this result, our finding in the present study of VEU times during RV apical pacing approximately half of those observed during LBBB with intrinsic conduction suggest that this group of patients may have less to gain from CRT than patients with LBBB.

Clinical implications for cardiac resynchronization therapy

Our findings have potentially important implications for patients with LV impairment who receive high percentages of RV pacing. The finding that the majority of patients in our study had significantly smaller reductions in VEU time may act to temper the enthusiasm for upgrading this group of patient to CRT. Only relatively small numbers of patients with RV pacing induced QRS prolongation have been included in randomised trials but those that have been randomised did not appear to benefit from upgrading to CRT.

There may be a potential role for electrocardiographic mapping as a means for screening chronically RV paced patients in order to identify individual patients who have prolonged VEU. Indeed, a subset of patients with high percentages of RVAP did have significantly prolonged VEU, the preferential target for CRT, and could be consider as good candidates for an upgrade strategy. In the present study 8 of the 24 patients had a VEU time of greater than

50ms. This assumption of course needs further investigation with appropriately powered randomized studies.

STUDY LIMITATIONS

The number of patients included in this study is modest; however, this is the largest study, with a within patient comparison, to date of detailed mapping of LV and RV electrical activation in heart failure patients during intrinsic rhythm (LBBB), RVAP and BVP. Furthermore, we have to admit the lack of mechanical study, of a clinical follow-up since this study was a within patient comparison and it is not admissible to implant LBBB patients with only RV pacing. No patients with septum or infundibular RV lead position have been included in the present study. Thus, we could not conclude on a potential difference in electrical epicardial activation pattern between different RV pacing sites. Since, only patients with LBBB were included in the present study we could not conclude to potential similarities or differences of epicardial electrical activation patterns during RVAP between patients with or without LBBB. Finally, the present study does not provide determinant data to answer the difficult question on the differences between chronic and de-novo RV pacing patients. In the BLOCK HF study²⁰, there was an improvement in terms of primary outcome in the group BIV versus the group RV pacing (de-novo pacing). In the present study, we also observed a significant improvement in terms of VEU and LVTAT between BV and RV pacing. However, this improvement was not “spectacular” and was significantly less than versus LBBB (lesser level of dyssynchrony at baseline during RV pacing versus LBBB). The question of the choice between RV and BIV pacing during de-novo implantation in requiring patients (complete AV block) is difficult and not easy to answer since the very recent BIOPACE trial results.

CONCLUSION

RV apical pacing results in important differences in ventricular activation pattern compared with native conduction with LBBB and the response to BVP also differs. The assumption that these 2 activation sequences are similar is not confirmed in the present study, suggesting potential differences in response after CRT. The RV pacing group may have less to gain from the addition of an LV lead; our study provides a possible explanation for the lack of response, which has been observed in the small number of patients who have been assessed in randomised control trials. Screening patients who receive high percentages of RV pacing with electrocardiographic mapping may be considered in future studies assessing the impact of upgrading chronically RV paced patients to CRT.

ACKNOWLEDGMENTS

None

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The present study highlights important differences in terms of electrical activations between LBBB and RV apical pacing. These differences result in a less important inter ventricular dyssynchrony during RV apical pacing compared to LBBB [RV apical pacing induce a more important RV total activation time compared to LBBB without any difference in LV total activation time; ventricular electrical uncoupling (VEU) was half during RV apical pacing]. Thus, RV apical pacing is not always deleterious in term of electrical dyssynchrony and may be less pejorative compared to LBBB. Less electrical dyssynchrony have to be corrected by bi-ventricular pacing during RV apical pacing compared to LBBB. The present study may help clinicians to better understand electrical dyssynchrony induced by RV apical pacing. Thus epicardial electrical activation mapping may be helpful to identify RV chronically paced patients with high levels of electrical interventricular dyssynchrony ($VEU > 50$ ms). A better response to bi-ventricular pacing might be observed in such patients after an upgrade strategy. Further studies are needed to validate this strategy.

TABLES

TABLE 1. Activation times during sinus rhythm (LBBB), right ventricular apical pacing and bi-ventricular pacing.

Parameter	LBBB (n=24)	RVAP (n=24)	BiV (n=24)	p-value 1 (LBBB vs. RVAP)	p-value 2 (BiV vs. RVAP)	p-value 3 (BiV vs. LBBB)
<i>LVTAT</i> (ms)	103 ± 22	116 ± 27	97 ± 19	0.06	<0.01	0.54
<i>RVTAT</i> (ms)	46 ± 21	69 ± 17	76 ± 15	<0.001	0.30	<0.001
<i>TAT</i> (ms)	129 ± 19	130 ± 23	103 ± 18	1	<0.001	<0.001
<i>VEU</i> (ms)	73 ± 12	38 ± 21	6 ± 28	<0.001	<0.001	<0.001

LBBB: left bundle branch block; LVTAT: left ventricular total activation time; RV BK: Right Ventricle breakthrough; RVAP: right ventricular apical pacing; RVTAT: right ventricle total activation time; TAT: total activation time; VEU: ventricular electrical uncoupling.

p-value 1: comparison for each parameter between LBBB and RVAP.

p-value 2: comparison for each parameter between RVAP and BiV pacing.

p-value 3: comparison for each parameter between LBBB and BiV pacing.

FIGURE LEGENDS**FIGURE 1.**

A. Epicardial electrical activation map showing a posterior line of slow conduction between red and purple plots (e.g. 60 ms). B. Local epicardial activation times were recorded from the onset of the QRS (black solid line) to the maximal negative slope of each unipolar electrogram (dotted line).

FIGURE 2.

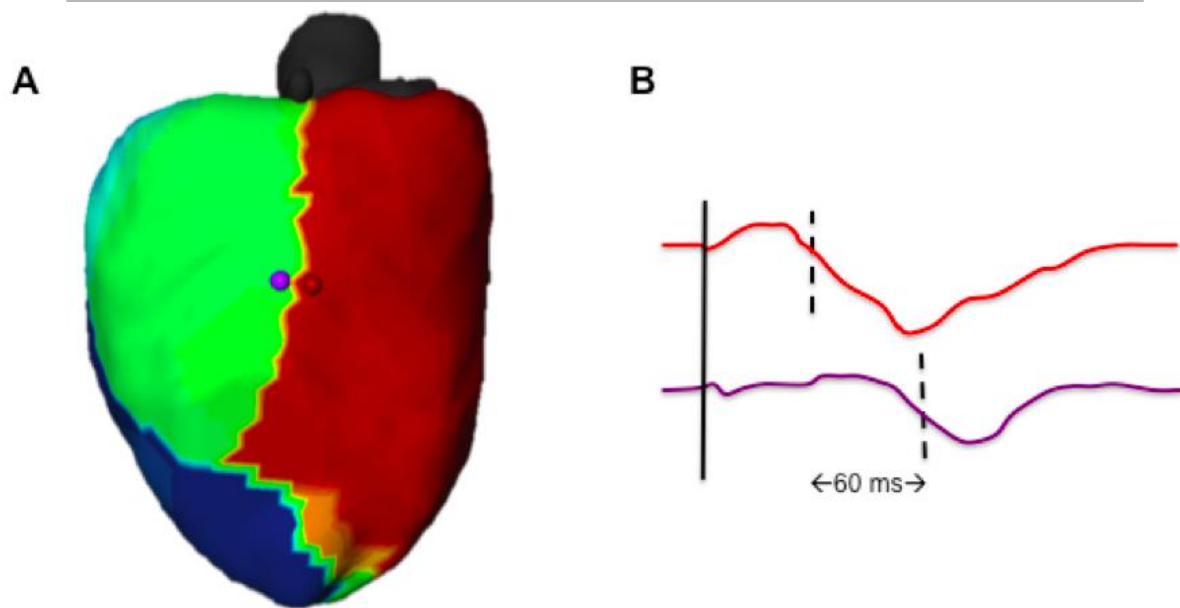
There were some similarities between LBBB and RVAP patients: 1 RV breakthrough, no LV breakthrough, and LV base as the latest activated area. However there were also differences: simultaneous apical activation of both ventricles by RVAP, different lines of slow conduction.

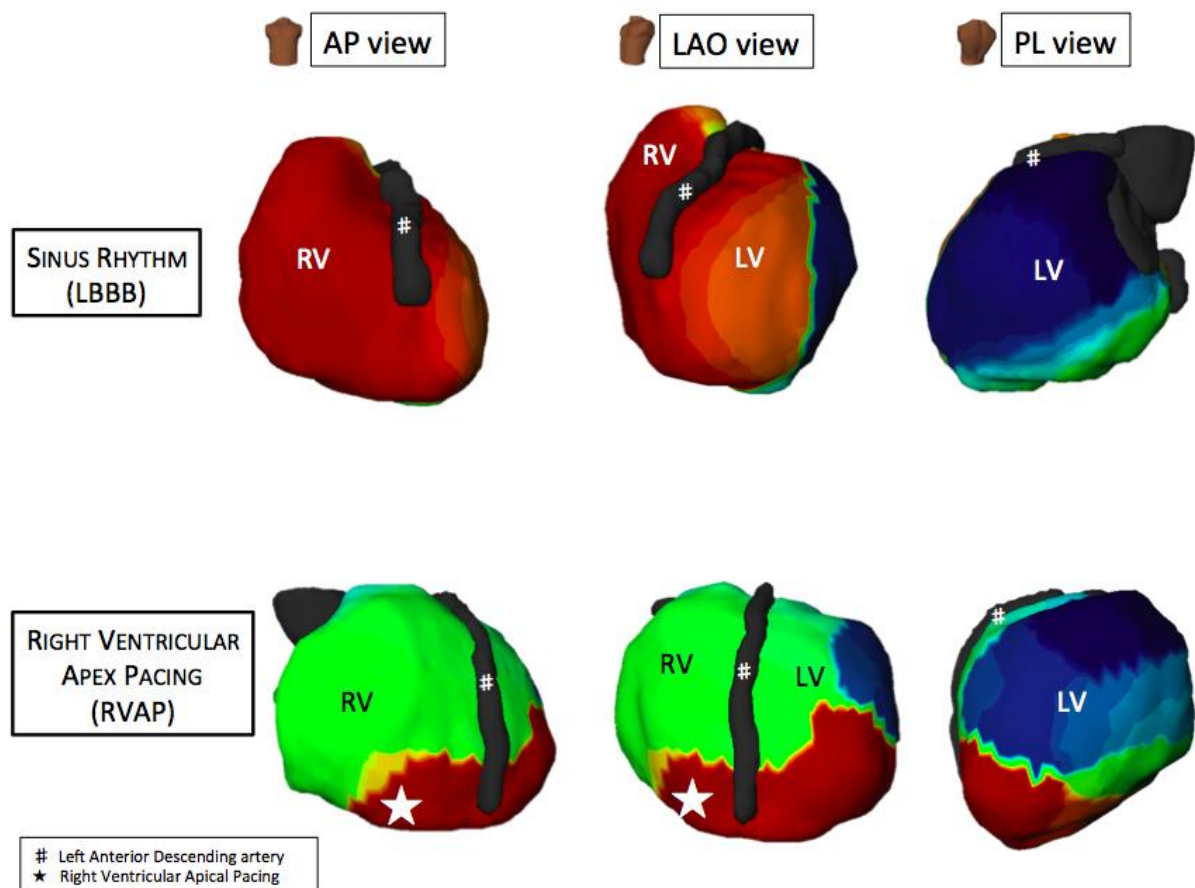
AP: Anteroposterior; LAO: Left anterior oblique; LBBB: Left bundle branch block; LV: Left ventricle; PL: posterolateral; RV: Right ventricle; RVAP: right ventricle apical pacing. #: Left anterior descending artery; The star represent the RV pacing site.

FIGURE 3.

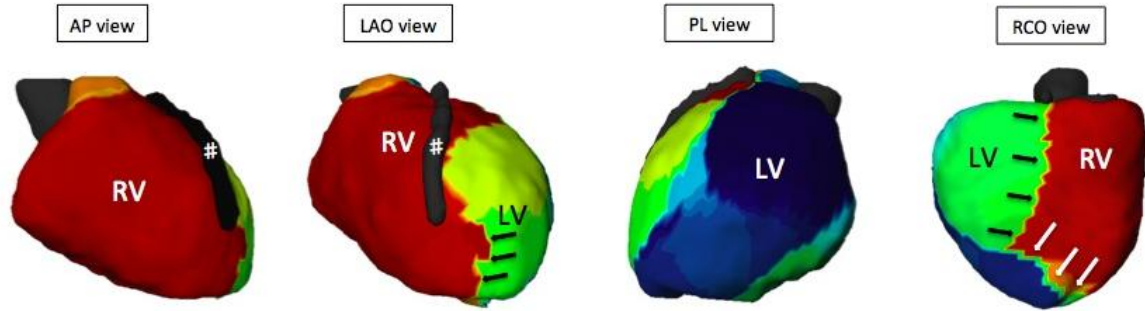
We observed in RVAP patients RV curvilinear lines of slow conduction (black and white arrows) around RV pacing site and several orientations (horizontal and base-to-apex) of LV Lines of slow conduction (black and white arrows). We observed more and longer LV Lines of slow conduction in LBBB patients with only a base-to-apex orientation.

LBBB: Left bundle branch block; LV: Left ventricle; RV: Right ventricle; RVAP: right ventricle apical pacing. #: Left anterior descending artery; The star represent the RV pacing site.

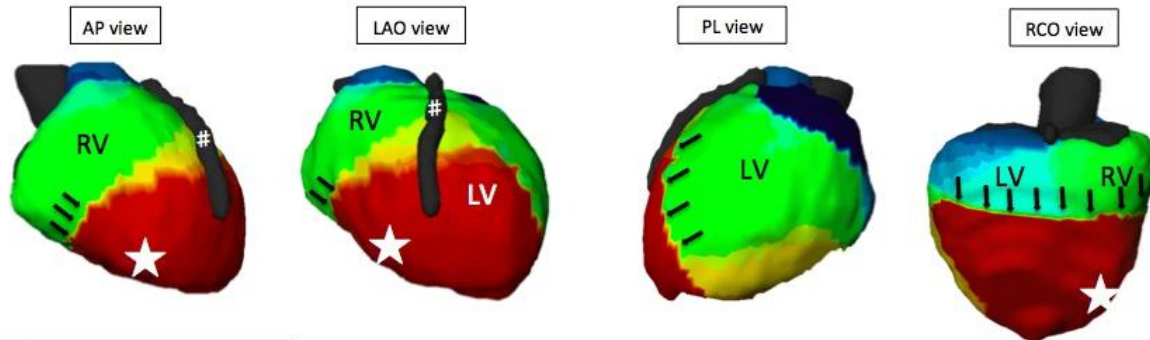




LV lines of slow conduction in LBBB



RV and LV lines of slow conduction in RVAP



Left Anterior Descending artery
★ Right Ventricular Apical Pacing

10 EVALUATION DE L'ASYNCHRONISME ELECTRIQUE INDUIT PAR LA STIMULATION BIVENTRICULAIRE : IMPLICATIONS POUR LA SELECTION DES PATIENTS ET L'AMELIORATION DE LA THERAPIE.*

*Ploux S, Eschalier R, Whinnett Z, et al Electrical dyssynchrony induced by biventricular pacing: implications for patient selection and therapy improvement. Under revision in *Heart Rhythm Journal*.

10.1 INTRODUCTION :

Nous avons vu que la CRT a été validée comme traitement de l'insuffisance cardiaque à fraction d'éjection altérée associée à un élargissement du QRS > 120 ms. Dans la gamme des patients à QRS larges (> 120 ms), certains substrats électriques sont plus favorables que d'autres ; ainsi les patients présentant un bloc de branche gauche sont reconnus comme bons candidats.⁶⁴ Parmi ces BBG, le taux et le degré de réponse sont néanmoins variables. A contrario les « non BBG » ne semblent pas tirer bénéfice de la stimulation BIV en dépit de l'élargissement du QRS. Des récentes études suggèrent même que pour certains, la CRT pourrait avoir un effet délétère.⁶⁵⁻⁶⁷ A la lumière de ces données se pose la question de savoir si l'activation électrique induite par la stimulation BIV diffère en fonction du substrat sur lequel elle est appliquée. A notre connaissance, les conséquences de la stimulation BIV sur l'asynchronisme cardiaque en fonction du substrat ne sont pas connues. Dans une large population d'insuffisants cardiaques (n=62) présentant des durées de QRS variables (incluant QRS fins, NICD et BBG) nous avons étudié la réponse hémodynamique aiguë à la stimulation BIV en relation avec le degré d'asynchronisme électrique (évalué par ECM) de base et induit par la stimulation BIV.

10.2 RESULTATS

10.2.1 Activation

La séquence d'activation induite par la stimulation BIV n'était pas dépendante du substrat électrique sous-jacent. Ainsi il était impossible, a posteriori, de reclasser les patients en QRS fins, NICD ou BBG au regard de leur cartes d'activation en stimulation BIV. Bien que spécifiques à chaque patient, ces cartes présentaient des caractéristiques communes. A droite comme à gauche, la primo activation (émanant des sondes) était excentrique limitée par un périmètre de conduction lente définissant un premier disque (ou une ellipse) de primo activation de rayon variable. Ce périmètre de conduction lente pouvait être complet ou incomplet. Parfois, ces aires de primo activation droite et gauche fusionnaient. Au-delà de ces zones la vitesse de conduction tendait à augmenter (espacement des isochrones) à moins que les nouvelles lignes de conduction lente n'apparaissent (51% des patients). Dans ce cas les lignes n'avaient ni longueur ni orientation spécifique, elles n'avaient aucune caractéristiques de celles que l'on pouvait (le cas échéant) observer en conduction spontanée. Il résulte de ces observations que les paramètres d'asynchronismes n'étaient en moyenne pas significativement différents dans les trois groupes de patients : QRS fins, NICD et BBG. La stimulation BIV induit un nouvel état d'asynchronisme électrique globalement constant quel que soit le substrat électrique sous-jacent. Ainsi les patients à QRS fins voyaient leurs paramètres d'asynchronisme (TAT, LVTAT, RVTAT, VEU) significativement aggravés ; les patients présentant un NICD voyaient leur RVTAT et LVTAT aggravés ; seuls les BBG avaient une réduction significative de TAT, LVTAT et VEU.

10.2.2 Relation dyssynchronie/hémodynamique

Les trois paramètres TAT, LVTAT et VEU mesurés lors de l'activation spontanée étaient fortement corrélés aux changements de $dP/dt_{\max}VG$ induits par la stimulation BIV. VEU ($r=0.79$, $p<.001$) obtenait une meilleure corrélation que TAT ($r=0.67$, $p<0.001$), LVTAT ($r=0.59$, $p<0.001$) ou que la durée du QRS ($r=0.67$, $p<0.001$) - $p<0.05$ pour chaque comparaison avec VEU.

Les paramètres d'asynchronisme évalués en stimulation BIV étant similaires dans les trois groupes de patients, les corrélations entre ces différents paramètres et les changements induits de $dP/dt_{\max}VG$ étaient soit nulles soit très faibles.

Les changements relatifs des paramètres TAT, LVTAT et VEU entre conduction spontanée et stimulation BIV étaient fortement corrélés aux changements de $dP/dt_{\max}VG$ induits par la stimulation BIV. Les coefficients de corrélation pour ΔTAT , $\Delta LVTAT$ and ΔVEU étaient respectivement de 0.71, 0.69, and 0.69 (tous $p < 0.001$).

10.2.3 Répondeurs vs nonrépondeurs

Vingt et un patients étaient hémodynamiquement répondeurs au seuil de 10% d'augmentation de $dP/dt_{\max}VG$. Ces patients présentaient des paramètres d'asynchronisme électrique de base significativement plus importants que les non répondeurs ($p < 0.001$ pour la comparaison de TAT, LVTAT et VEU). Un $VEU > 50ms$ discriminait les répondeurs avec une sensibilité de 100% et une spécificité de 78%.

Sous stimulation BIV les répondeurs présentaient une réduction significative d'asynchronisme électrique sur ces trois paramètres, alors que les non-répondeurs souffraient d'une prolongation de TAT et LVTAT. La réduction relative de VEU (ΔVEU) était plus importante pour les répondeurs que les non-répondeurs. Certain de ces derniers présentaient même une aggravation de ce paramètre (augmentation du délai VG sous stimulation BIV).

Plusieurs résultats de cette étude méritent d'être discutés :

Nous confirmons dans cette étude que l'asynchronisme électrique est fortement corrélé à la réponse hémodynamique dépendante de la stimulation BIV.

La stimulation BIV induit un nouvel état d'asynchronie globalement stable et indépendant du substrat électrique sous-jacent. Ce niveau d'asynchronie se situe quelque part au-dessus du niveau d'asynchronisme moyen des patients NICD et en dessous du niveau d'asynchronisme des patients avec BBG.

Une amélioration hémodynamique est prévisible tant que l'asynchronisme de base excède l'asynchronisme induit par la stimulation BIV. Inversement la stimulation BIV va détériorer l'asynchronisme de certains patients insuffisamment désynchronisés à l'état de base. Cette désynchronisation va se traduire par une diminution des performances contractiles VG et

éventuellement par une aggravation du pronostic. C'est pourquoi nous avons parlé de d'électropathie induite par la CRT pour décrire ce phénomène. En effet, deux essais randomisés contrôlés évaluant l'efficacité de la resynchronisation chez les patients à QRS fins ont été récemment interrompus pour des raisons de sécurité (aggravation du test de marche de 6min et tendance à l'augmentation des hospitalisations pour les patients resynchronisés à QRS fins dans l'essai LESSER-EARTH et majoration de 81% du taux de mortalité dans le groupe CRT pour l'étude ECHO-CRT).^{65,66} Plus inquiétant encore sont les résultats d'analyse en sous-groupes de l'étude MADIT-CRT prolongée sur 7 ans chez plus de 800 patients. Dans cette étude la CRT entraînait une réduction de 41% des décès chez les patients présentant un BBG alors que chez les non-BBG (QRS>130ms), la même « thérapie » provoquait un excès de mortalité : HR1.57 (1.03-2.39); p=0.04. Nos résultats suggèrent que cet excès de mortalité soit relié à une électropathie induite: en effet, un certain nombre de nos patients avec NICD avaient des valeurs de LVTAT ou VEU comparable à celle des patients à QRS fins, et en moyenne dans ce groupe la stimulation BIV aggravait le LVTAT.

Enfin nous avons montré que si la stimulation BIV était très efficace dans la correction du VEU, son action sur les temps d'activation VG et totaux était modérée, avec des valeurs de TAT, LVTAT très éloignées des valeurs rencontrées pour les QRS fins. Hors la réduction des temps d'activation semble être un paramètre important puisque d'une part leurs variations (relative à la conduction spontanée) sont corrélées aux changements de $dP/dt_{\max}VG$, et que d'autre part leurs prolongements (chez les QRS fins par exemple) s'accompagnent d'une détérioration hémodynamique en dépit d'une réduction du VEU. Ainsi il est possible d'envisager une optimisation de la resynchronisation visant à réduire les temps d'activation VG et totaux.

**ELECTRICAL DYSSYNCHRONY INDUCED BY BIVENTRICULAR PACING:
IMPLICATIONS FOR PATIENT SELECTION AND THERAPY IMPROVEMENT**

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Funding Sources:

The study was supported by the French Government, Agence National de la Recherche au titre du programme Investissements d'Avenir (ANR-10-IAHU-04). J. Lumens received a grant within the framework of the Dr E. Dekker program of the Dutch Heart Foundation (NHS-2012T010).

Disclosures:

M. Hocini, P. Jaïs and M. Haïssaguerre are stock owners of CardioInsight Technologies Inc (Cleveland, OH). CardioInsight Technologies provided the electrocardiographic mapping system for free. This sponsor had no access to data management or data analysis.

Word count: 4971

ABSTRACT***Background***

It is unknown whether the resynchronizing effect of biventricular pacing (BVP) varies among patients depending on the underlying electrical substrate.

Methods

High resolution ventricular electrocardiographic mapping with invasive measurement of Left Ventricular (LV) dP/dtmax were performed during baseline activation and during BVP in 61 heart failure patients with various conduction delays: 13 narrow QRS (<120ms), 22 nonspecific intraventricular conduction disturbance and 26 left bundle branch block. Electrical dyssynchrony, both during baseline activation and BVP, was quantified by total and LV activation times (TAT and LVTAT) and by ventricular electrical uncoupling (VEU = mean LV – mean RV activation time). Response to BVP was defined as a $\geq 10\%$ LVdP/dtmax increase.

Results

The electrical activation pattern during BVP was similar for all patient groups and, hence, not dependent on the baseline conduction disturbance present. During BVP, TAT, LVTAT and VEU

were similar for all groups and correlated not or weakly with the change in LVdP/dtmax. In contrast, the changes in electrical dyssynchrony correlated significantly with the change in LVdP/dtmax: Spearman's $r=0.71$, 0.69 , and 0.69 for ΔTAT , $\Delta LVTAT$ and ΔVEU , respectively (all $p<0.001$). Responders showed higher baseline dyssynchrony levels and BVP-induced dyssynchrony reduction than nonresponders (all $p<0.001$); in nonresponders BVP worsened activation times compared to baseline.

Conclusion

BVP does not eliminate electrical dyssynchrony but rather brings it to a common level independent of the patient's underlying electrical substrate. As a consequence, BVP is of benefit to dyssynchronous patients but not to patients with insufficient electrical dyssynchrony in whom it induces an iatrogenic electropathy.

Key words: cardiac resynchronization therapy; electrical mapping; electrocardiographic mapping; hemodynamic; heart failure; pacing; left bundle branch block; Nonspecific Intraventricular Conduction Disturbance

ABBREVIATIONS

BVP : Biventricular Pacing

CRT: Cardiac Resynchronization Therapy

LBBB: Left Bundle Branch Block

LV: Left Ventricle

LVdP/dt_{max}: maximal rate of systolic LV pressure rise

LVTAT: Left Ventricular Total Activation Time

NICD: Nonspecific Intraventricular Conduction Disturbance

RV: Right Ventricle

TAT: Total Activation Time (both ventricles)

VEU: Ventricular Electrical Uncoupling

INTRODUCTION

Biventricular pacing (BVP) is known to induce hemodynamic and clinical improvements as well as left ventricular (LV) reverse remodeling in heart failure patients with depressed LV ejection fraction and conduction disorders.^{1,2} Cardiac resynchronization therapy (CRT) is generally assumed to act by restoring synchrony of the ventricular activation, and the baseline QRS duration has historically been considered as the hallmark of electrical dyssynchrony.^{3,4} However, patient selection based on QRS duration is associated with a substantial rate of nonresponse. The concept of resynchronization is challenged by the observation that for patients with similar QRS duration, those with left bundle branch block (LBBB) respond significantly better than those with nonspecific intraventricular conduction disturbance (NICD).^{5,6} This difference may be explained by a differential effect of BVP depending on the underlying baseline electrical substrate. This hypothesis is buttressed by the recent reports showing that in non-LBBB patients, BVP can be inefficient or even harmful.⁷⁻¹⁰ An improved mechanistic understanding of the limitations and beneficial effects of current methods for delivering BVP therapy is therefore required, 1) to identify targets for improving this therapy and 2) to avoid worsening of the patients prognosis.

In the present study, we specifically address the electrical consequences of BVP in relation to the patients' underlying electrical substrates and set out to determine whether this influences the magnitude of the hemodynamic response to this therapy. To this purpose, we performed electrocardiographic mapping of both ventricles together with invasive hemodynamic measurements before and after BVP in a population of heart failure patients covering a wide spectrum of conduction disorders, i.e., narrow QRS duration, NICD, and LBBB.

METHODS

This study is different in design from the studies that previously reported an observational association between mechanical dyssynchrony and long term outcomes, which was later found to be not therapeutically valid when tested formally by prospective randomized trials. Instead our study carries out invasive measurements of hemodynamic response to BVP in relation to detailed electrical measurements of dyssynchrony. The conduct of the study conformed to the principles outlined in the declaration of Helsinki on research in human subjects. All patients granted their written approval to participate in the study, which was approved by the institutional ethics committee.

PATIENT POPULATION

The study population consisted of a cohort of 61 patients scheduled for CRT-device implantation. To obtain a large range of electrical ventricular dyssynchrony we included, between September 2009 and June 2013, patients with: narrow QRS duration (<120 ms, 13 patients, 21%), NICD (22 patients, 36%), or LBBB (26 patients, 43%) on the 12-lead surface ECG. Intraventricular conduction disturbances were defined according to the most recent AHA/ACCF/HRS criteria.¹¹ All patients fulfilled the following criteria: New York Heart Association (NYHA) functional class II, III or IV despite optimal medical therapy, ejection fraction $\leq 35\%$ and sinus rhythm during the experiments. Second or 3rd degree atrioventricular block, severe aortic valve stenosis, or LV intracavitary thrombus were criteria for exclusion. In the narrow QRS group, 6 patients had a bradycardia indication for pacing (3 paroxysmal AV block and 3 brady-

tachy syndrome with slow ventricular conduction) while 7 patients had previous persistent AF with uncontrolled heart rate and were candidate to AV node ablation.

Mean age was 66 ± 10 years, 49 were male (80%), 28 (46%) had an ischemic cardiomyopathy (defined as a history of myocardial infarction or prior revascularization), 15 (25%) patients were in NYHA Class II, 45 (74%) in Class III, and 1 (2%) in Class IV. Mean LV ejection fraction, assessed by echocardiography, was $27 \pm 5\%$ and mean QRS duration as derived from the 12-lead surface ECG was 142 ± 27 ms. More detailed analyses of the baseline electrical substrate of 18 LBBB and 14 NICD patients are available elsewhere.¹²

The 61 patients were implanted with a cardiac resynchronization therapy-defibrillator via a percutaneous transvenous approach. The RV lead was implanted preferentially at the RV apex. The position of the LV lead depended on the coronary venous anatomy, lead stability, pacing threshold (sites with phrenic nerve capture were avoided). Within 72 hours of implantation, every patient underwent a hemodynamic and an electrocardiographic mapping assessment.

ACUTE HEMODYNAMIC STUDIES

Continuous invasive LV pressure measurement was performed using a micromanometer (Radi Medical Systems; St Jude Medical, St. Paul, MN) placed in the LV cavity via retrograde transaortic catheterization. The LV pressure signal was used to measure maximal rate of systolic LV pressure rise ($LVdP/dt_{max}$) during baseline sinus rhythm and during atrial sensed biventricular stimulation (VDD mode). The atrio-ventricular (AVD) delay was set to 80ms. In cases of sinus bradycardia (rate < 45bpm) or frequent extrasystoles, LV pressure during baseline and BVP were alternatively measured in AAI and DDD mode, respectively (same atrial pacing rate). In these cases the AVD was set to 100ms (a compromise between the need for AVD extension in the

atrial paced condition and the need for AVD reduction at higher pacing rates). VV delay was programmed to 0ms. Pressure data were recorded after a 30-second period of hemodynamic stabilization. $\text{LVdP/dt}_{\text{max}}$ was calculated as the average over a 10-second recording that was free from ventricular or supraventricular extrasystoles. Hemodynamic response was assessed by the BVP-induced %-change of $\text{LVdP/dt}_{\text{max}}$. Patients demonstrating a $\geq 10\%$ increase in $\text{LVdP/dt}_{\text{max}}$ were defined as hemodynamic responders to CRT.^{3,13}

NONINVASIVE MAPPING OF ELECTRICAL ACTIVATION

Ventricular activation maps were acquired during baseline activation and BVP (with the same pacing settings as during the hemodynamic assessment) using a noninvasive high-resolution electrocardiographic mapping system (ECVUE™, CardiInsight Technologies Inc, Cleveland, Ohio). As previously described in detail, body surface potentials were recorded from 252 sites around the entire surface of the torso.^{12,14} A thoracic computed tomography scan was acquired with the electrodes attached to the patient. The body surface potentials and computed tomography images were then combined and processed to reconstruct 1500 epicardial unipolar electrograms. Local ventricular activation times were calculated from the onset of the QRS (baseline) or the pacing spike (BVP) to the maximal negative slope of each unipolar electrogram. An epicardial breakthrough site was defined as the earliest location identified on the isochrone map. A line of slow conduction was recorded if the activation times of adjacent points on either side of this line differed by more than 50 ms. The following electrical dyssynchrony indices were derived from the maps:

- TAT_{SR} and TAT_{BVP} : Total Activation Time, defined as the time difference (ms) between the earliest and the latest site of activation on the entire ventricular epicardium (left and right ventricle (RV)) during baseline activation (SR) or biventricular pacing (BVP). ΔTAT was $TAT_{SR} - TAT_{BVP}$ (ms).
- $LVTAT_{SR}$ and $LVTAT_{BVP}$: LV Total Activation Time, defined as the time difference (ms) between the earliest and the latest site of activation on the LV epicardium only, during baseline activation (SR) or biventricular pacing (BVP). $\Delta LVTAT$ was $LVTAT_{SR} - LVTAT_{BVP}$ (ms).
- VEU_{SR} and VEU_{BVP} : Ventricular Electrical Uncoupling, defined as mean LV activation time minus mean RV activation time (ms) during baseline activation (SR) or biventricular pacing (BVP). ΔVEU was $VEU_{SR} - VEU_{BVP}$ (ms).

STATISTICAL ANALYSIS

We have presented categorical variables as counts (percentages) while continuous variables were expressed as mean (SD) or as median (minimum-maximum). Comparisons of TAT, LVTAT and VEU between groups were performed using a Kruskal-Wallis test. Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons. Within each group, we compared SR and BVP data with a paired t-test. Responders and nonresponders were compared using a Mann-Whitney U test. The relationships between $LVdP/dt_{max}$ and TAT, LVTAT, or VEU (SR, BVP or Δ) were assessed by using the Spearman correlation coefficient (r_s). Partial correlations that accounted for SR values were estimated for Δ values of TAT, LVTAT and VEU. Correlations were compared using the T2 method

recommended by Steiger.¹⁵ A p -value <0.05 was considered statistically significant for all tests.

Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

ELECTROCARDIOGRAPHIC MAPPING OF VENTRICULAR ACTIVATION DURING BVP

Figure 1 shows activation maps during baseline activation and during BVP for one patient of each subgroup. Figure 2 summarizes average values of TAT, LVTAT and VEU during baseline activation and BVP for all three patient groups.

The electrical activation sequence observed during biventricular pacing was not dependent on baseline conduction characteristics and was patient specific (figure 1). Thus, we were unable to blindly classify the BVP maps according to their baseline conduction characteristics (narrow QRS, NICD or LBBB). Nevertheless, some common features were recognized. First, we observed activation originating from two locations corresponding to the respective RV and LV pacing site. RV activation onset usually preceded initial LV activation by 6 ± 18 ms on average ($p=0.3$ between the 3 groups). From each of these two breakouts activation spread radially, and was not affected by the lines of slow conduction when present during baseline activation. On the LV surface, the eccentric front of activation encountered a new curved line of slow activation with variable length and radius of curvature, delineating a primary area of fast activation. These lines were seen in 51 (84%) patients independently of their baseline conduction characteristics. We observed the same phenomenon less frequently on the RV surface (37 patients, 61%). The radius of the curves were similar to that observed in the LV, however were shorter in length. The primary area of RV activation frequently reached the LV epicardium, producing in some

cases coalescence between the areas of primary RV and LV activation. Beyond these islands of early activation the apparent speed of activation tended to increase (widely spaced isochronal lines), unless additional conduction delays appeared as occurred in 31 patients (51%). Such remote lines of slow conduction showed no consistency in shape or orientation.

During BVP, the electrical dyssynchrony indexes TAT_{BVP} , $LVTAT_{BVP}$ and VEU_{BVP} were not significantly different between the three patient subgroups (Figure 2). As a result narrow QRS patients showed a significant increase in both TAT and LVTAT relative to baseline conduction, and NICD patients also showed a significant increase in LVTAT (Figures 2,3). Only the LBBB group presented a significant BVP-induced reduction in the three dyssynchrony parameters.

RELATIONSHIP BETWEEN ELECTRICAL DYSSYNCHRONY AND HEMODYNAMIC RESPONSE TO BVP

Hemodynamic measurements were successfully obtained in 58 patients. Onset of complete atrio-ventricular block during the procedure for one and excessive artifacts on the hemodynamic trace for two others prevented analysis in three patients. Baseline QRS duration was associated with the changes in $LVdP/dt_{max}$ induced by BVP ($r_s=0.67$; $p<0.001$).

When considering all patients together, all three indices of baseline electrical dyssynchrony were correlated to the changes in $LVdP/dt_{max}$ induced by BVP relative to baseline conduction (Figure 4). Spearman correlation coefficients for TAT_{SR} , $LVTAT_{SR}$ and VEU_{SR} were: 0.67, 0.59, and 0.79 respectively (all $p<0.001$). The association with the changes in $LVdP/dt_{max}$ was stronger for VEU_{SR} than TAT_{SR} ($p<0.03$ vs VEU_{SR}), $LVTAT_{SR}$ ($p<0.01$ vs VEU_{SR}) or QRS duration ($p=0.04$ vs VEU_{SR}).

In contrast, during BVP the indices of electrical dyssynchrony showed little or no correlation with the changes in $\text{LVdP}/\text{dt}_{\text{max}}$ as illustrated in Figure 5. Spearman correlation coefficients for TAT_{BVP} , $\text{LVTAT}_{\text{BVP}}$ and VEU_{BVP} were: -0.28 ($p=0.03$), -0.24 ($p=0.08$) and -0.12 ($p=0.38$) respectively.

In the whole patient population there was a significant correlation between the changes in the 3 electrical dyssynchrony parameters and the changes in $\text{LVdP}/\text{dt}_{\text{max}}$ induced by BVP (Figure 6). Spearman correlation coefficients for ΔTAT , ΔLVTAT and ΔVEU were respectively: 0.71, 0.69, and 0.69 (all $p<0.001$). In order to refine the understanding of this relationship we calculated partial correlation coefficients that account for the TAT_{SR} , LVTAT_{SR} and VEU_{SR} values: $r_s'=0.33$, ($p=0.01$) for ΔTAT ; $r_s'=0.44$, ($p=0.001$) for ΔLVTAT ; $r_s'=0.29$, ($p=0.03$) for ΔVEU .

In summary, the hemodynamic response to BVP is correlated strongly with the baseline electrical dyssynchrony and to a lesser extent with the change in electrical dyssynchrony between BVP and baseline activation.

ELECTRICAL DETERMINANT OF THE HEMODYNAMIC RESPONSE

At a 10% increase level of $\text{LVdP}/\text{dt}_{\text{max}}$ we found 21 responders (1 narrow QRS, 2 NICD and 18 LBBB) and 37 nonresponders. Responders showed higher levels of baseline electrical dyssynchrony than nonresponders ($p<0.001$ for TAT_{SR} , LVTAT_{SR} and VEU_{SR}). All responders had a $\text{VEU}\geq 50\text{ms}$ whereas only 22% of nonresponders were above this 50ms cutoff (100% sensitivity; 78% specificity). (Table 1)

Responders and nonresponders presented similar dyssynchrony levels during BVP ($p=\text{ns}$ for TAT_{BVP} , $\text{LVTAT}_{\text{BVP}}$ and VEU_{BVP}), whereas changes in electrical dyssynchrony were significantly different between both patient groups. Across the group as a whole mean TAT and LVTAT

decreased compared to baseline conduction in responders (-32 ± 20 ms for TAT, -17 ± 20 ms for LVTAT), while they increased in nonresponders ($+21 \pm 32$ ms for TAT; $+30 \pm 28$ ms for LVTAT; $p < 0.001$ for both). In only one responder did we observe a prolongation in TAT with BVP compared to baseline conduction, while three patients were responders despite LVTAT prolongation during BVP. All responders showed a VEU reduction ≥ 28 ms and overall a greater reduction in VEU than nonresponders ($p < 0.001$). For some nonresponders the VEU was even increased (negative value of Δ VEU) meaning that the relative delay of the LV was worsened with BVP compared to baseline conduction.

DISCUSSION

Based on detailed ventricular activation mapping, during both baseline conduction and BVP, this study casts some light on mechanisms through which BVP alters cardiac performance.

First, the ventricular activation time and pattern (ventricular electrical uncoupling) produced during BVP is not dependent on the baseline ventricular conduction characteristics. BVP produces similar levels of electrical synchrony (or dyssynchrony) regardless of the underlying electrical substrate.

Second, the main driver of acute hemodynamic response is the magnitude of change in ventricular electrical uncoupling and ventricular activation time. Since BVP results in similar ventricular activation characteristics regardless of the underlying substrate, improvements or worsening in function are mostly determined by the severity of ventricular conduction impairment during baseline conduction.

SPECIFIC BASELINE ELECTRICAL ACTIVATION VERSUS COMMON BVP ACTIVATION BEHAVIOR

Independent of the underlying conduction disease, we observed similar activation behavior during pacing. A consistent phenomenon was the occurrence of curvilinear activation delays near the LV pacing site. Our results using non-invasive epicardial activation maps are consistent with previous findings using non-contact endocardial mapping in patients with LBBB.¹⁶ Using contact epicardial mapping in canines, Burgess et al. also demonstrated that these abrupt changes in uniformity of activation were solely the result of changes in pacing sites.¹⁷

Noteworthy these activation delays were less marked during endocardial pacing than during epicardial pacing. Although we did not test LV endocardial pacing we observed that these curves of activation delay were less frequent and shortest around the endocardial RV pacing site. If the endocardium seems to play a critical role, we don't have any information concerning the possible contribution of the Purkinje system, which has been found, again in healthy dogs, to be limited.¹⁸ We presume that if present, the Purkinje involvement was similar for narrow and wide QRS patients.

BASELINE RATHER THAN PACING-INDUCED ELECTRICAL DYSSYNCHRONY DETERMINES HEMODYNAMIC RESPONSE TO BIVENTRICULAR PACING

We observed linear relationships between the three baseline dyssynchrony parameters characterizing the baseline electrical substrate and the hemodynamic response to BVP. Once BV

paced, the strength of the association between electrical dyssynchrony and hemodynamic change dropped dramatically. Responders showed significantly higher baseline electrical dyssynchrony parameters than the nonresponders but similar degree of electrical dyssynchrony during BVP. This suggests that the differences observed between responders and nonresponders, with respect to change in electrical dyssynchrony from baseline conduction to BVP were mostly driven by the differences in baseline electrical dyssynchrony. In particular a baseline $VEU \geq 50ms$ was consistently observed in responders (sensitivity and negative predictive value of 100%) with 78% specificity. We have previously show in a prospective clinical trial that patients with a VEU_{SR} above 50ms had a 42 fold increase in the likelihood of being a responder ($p < 0.001$).¹²

HEMODYNAMIC RESPONSE TO BIV PACING ALSO DEPENDS ON THE QUALITY OF RESYNCHRONIZATION

If electrical dyssynchrony is a prerequisite to the hemodynamic response to BVP, the amount of dyssynchrony reduction also plays a role as shown in figure 6. Partial correlation coefficients (corrected for baseline electrical dyssynchrony) indicated that the electrical resynchronization is independently correlated to the hemodynamic response to BVP. Interestingly, among the three dyssynchrony parameters, only VEU was consistently reduced in CRT responders (table 1). CRT response could occur despite TAT or LVTAT increase. These results are in agreement with our finding that single-site LV pacing can be as beneficial for cardiac pump function as BVP, despite the lack of TAT and LVTAT reduction during single site LV pacing.¹⁹ Correction (or reversion) of a deleterious VEU appears thus as the best candidate for a fundamental mechanism driving CRT response. On the other hand, the observation that BVP could be associated with worsening of

hemodynamic function and with lengthening of electrical activation times (TAT and LVTAT) despite reduction in VEU (nonresponders, table 1), strengthen the importance of maintaining ventricular activation times short. In summary, we propose that the principal benefit of BVP is the correction of the VEU. The level of response may further be enhanced by the optimization of the total and LV activation times.

CLINICAL IMPLICATIONS:

IATROGENIC ELECTROPATHY

We clearly showed that the hemodynamic response to CRT was closely related to the baseline electrical dyssynchrony. All the responders fulfilled a minimum of electrical dyssynchrony. In particular, they all had a large VEU (≥ 50 ms), with no exception. CRT is an electrical therapy treating a significant electrical substrate.

BVP induced a new stage of electrical dyssynchrony, which was roughly homogeneous whatever the underlying conduction disease. The mean amount of dyssynchrony as assessed by our 3 parameters was somewhere in between the baseline dyssynchrony values for narrow and LBBB patients. Thus, the pacing induced dyssynchrony could be worse than the baseline condition, with a detrimental effect on the hemodynamic (Figures 1, 2, 3, 6, and 7). The deleterious effect of BVP in patients with little electrical dyssynchrony (narrow QRS) has recently been highlighted by the results of two multicenter randomized controlled trials. The LESSER-EARTH trial was prematurely stopped because of futility and safety concerns after 85 patients with QRS duration < 120 ms were randomized to CRT “on” or CRT “off”.⁷ In the treatment group, the 6-minute walk distance was significantly shorter at 12 months (-11 m versus 25 m; $p=0.01$), with a trend toward an increase in heart failure-related hospitalizations. In the Echo-CRT study, CRT-D was

randomly applied to patients with a narrow QRS duration(<130ms, mean QRS duration of 105ms) who were classified as having mechanical dyssynchrony using echocardiography.⁸ The data safety monitoring board terminated the trial prematurely because of an 81% higher mortality rate was observed in the CRT group. The proarrhythmic effect of CRT in this population was probably not the main explanation for this result since the number of ICD shocks did not differ between the CRT and the control group. Our observations in the current study provide an alternative explanation for these findings. We found that BVP actually results in more dyssynchronous electrical ventricular activation, when it is applied to patients with little or no electrical dyssynchrony (Figure 7). Therefore in patients with a narrow QRS duration BVP induces electrical dyssynchrony, which worsens cardiac function which would be expected to result in worse clinical outcomes.

Recent data from the extended MADIT-CRT trial suggests that the CRT-induced iatrogenic dyssynchrony may also be important in non-LBBB patients with a wide QRS duration.⁹ From the initial 1818 patients initially randomized to CRT with a defibrillator or defibrillator only, 854 were followed up to 7 years. There was a 41% reduction in the long-term risk of death among patients with left bundle-branch block who were randomly assigned to CRT, while non-LBBB patients (QRS \geq 130ms) showed a significant increase of death with the same “therapy” (hazard ratio 1.57 (1.03-2.39); p=0.04). This striking result may be explained by our observation that many patients with NICD actually have left ventricular activation times (as well as VEU) which are comparable to those observed in patients with narrow QRS duration on the 12 lead ECG (figure 4), especially those for whom the QRS widening reflect a RV delay (negative VEU). We

found that in the group as a whole BVP increased the LVTAT in patients with NICD (figure 2, panel B), an adverse effect that may impair clinical outcome. See also figure 3.

THE MISSED POTENTIAL OF CONVENTIONAL BVP

In this study we demonstrate that reducing ventricular activation time is an integral part of the mechanism through which BVP produces its beneficial effect. If BVP is applied to patients with minimal electrical dyssynchrony current methods for delivering BVP produces a prolongation in activation time which in turn has adverse hemodynamic consequences.

Our data also shows that BVP does not fully reverse the conduction impairment induced by LBBB, in fact it results in only modest reductions in LV activation time (Figure 2, B). Activation times with BVP are significantly longer than those observed during baseline conduction with a narrow QRS duration. Therefore there appears to be significant potential for improving resynchronization therapy. We believe efforts should be made to develop techniques to improve the delivery of ventricular resynchronization since they have a high likelihood of producing additional improvements in cardiac function.

PERSPECTIVES

Proper patient selection based on the baseline electrical dyssynchrony appears more important than ever, allowing discrimination of potential responders as well as identifying patients who are likely to be adversely affected by BVP. Reducing VEU appears to be a critical component of the mechanism through which BVP delivers its beneficial effect. We showed that VEU reduction was necessary for CRT response. However Δ TAT and Δ LVTAT were also correlated to changes in $LVdP/dt_{max}$, suggesting that faster activation times provide higher hemodynamic response.

Whether or not the hemodynamic response to BVP could be enhanced by optimization of the electrical resynchronization at the individual level deserves future investigation.

LIMITATIONS

The absence of RBBB patients in our population has magnified the value of the TAT parameter (same for the QRS duration). However LVTAT and VEU were insensitive to this selection bias. We used a relatively short AV delay to avoid fusion with the baseline activation. This allowed us to exclusively assess the effect of BVP but may differ from the clinical practice. The low response rate (36%) presented in this study is explained by the inclusion of patients with narrow QRS complex.

CONCLUSION

Hemodynamic response to BVP is strongly correlated to the changes in electrical dyssynchrony induced by BVP. These latter changes mostly depend on the baseline electrical dyssynchrony since BVP provided similar activation features whatever the underlying conduction disease.

Hemodynamic response can be expected as long as the amount of baseline electrical dyssynchrony exceeds the amount induced by BVP. Conversely, BVP may induce an iatrogenic electropathy in patients suffering from insufficient electrical dyssynchrony at baseline.

Considerable potential exists for improving the effectiveness of resynchronization therapy if methods can be developed to deliver better electrical ventricular resynchronization.

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TABLE

TABLE 1

Responders versus nonresponders: electrical dyssynchrony (median [min ;max]).

Parameter	Responders (n=21)	Nonresponders (n=37)	<i>p</i>
	Narrow: 1 /NICD:2 /LBBB: 18	Narrow: 12 /NICD:19 /LBBB: 6	
TAT_{SR}	136 [81;173]	86 [41;134]	<0.001
LVTAT_{SR}	118 [61;158]	72 [29;125]	<0.001
VEU_{SR}	72 [50;95]	35 [-41;86]	<0.001
TAT_{BIV}	101 [78;135]	111 [77;143]	0.12
LVTAT_{BIV}	96 [71;135]	107 [66;136]	0.23
VEU_{BIV}	8 [-32;42]	9 [-43;63]	0.85
ΔTAT	27 [-20;63]	-31 [-90;51]	<0.001
ΔLVTAT	21 [-23;47]	-34 [-82;19]	<0.001
ΔVEU	62 [28;118]	24 [-55;100]	<0.001

FIGURES

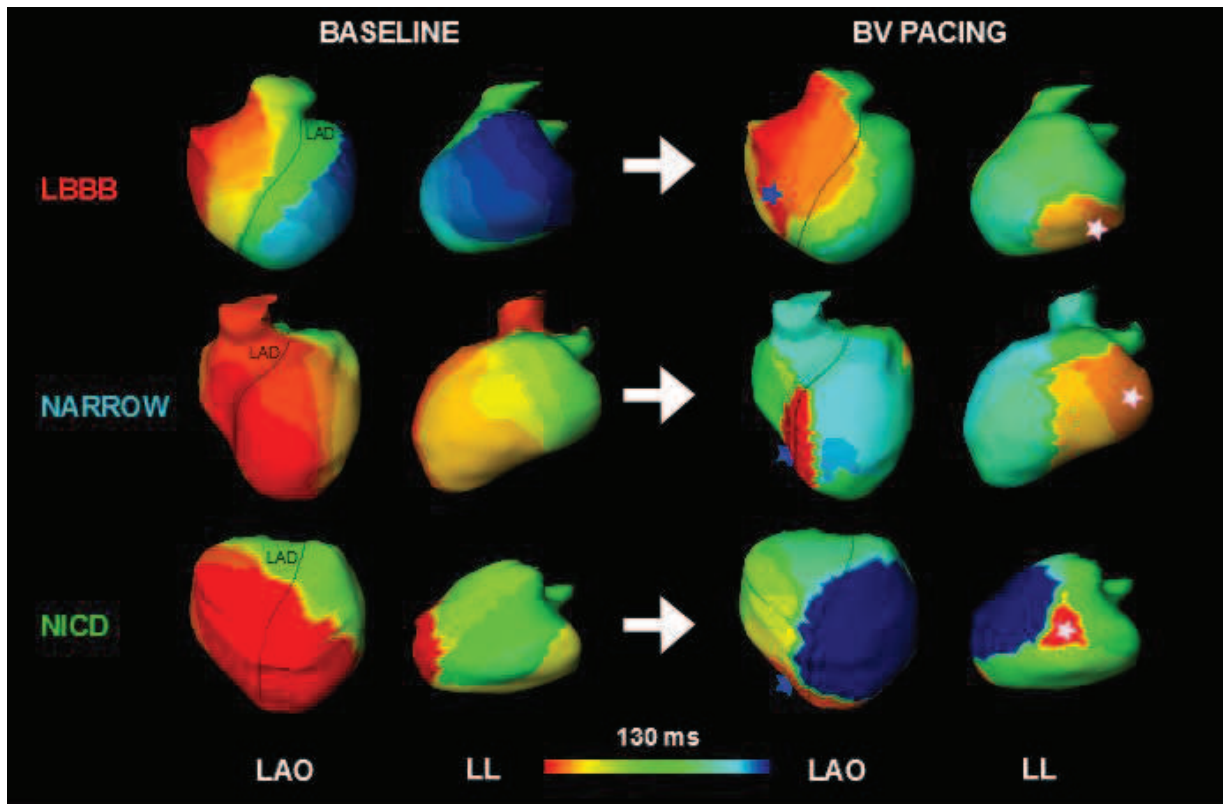


FIGURE1

Electrocardiographic maps of 3 patients during baseline conduction (left side, “baseline”) and BVP (right side, “BV pacing”). Top row: “LBBB”; patient with a LBBB (QRS duration: 160ms). Middle row: “narrow”; patient with a narrow QRS complex (QRS duration: 118ms). Bottom row: “NICD”; patient with a NICD (QRS duration: 130ms). For comparison purpose, all maps referred to the same relative scale of 130ms. LAO: left anterior oblique view. LL: left lateral view. Blue stars indicate RV pacing location. White stars indicate LV pacing location. LAD: left anterior descending artery. BVP results in alteration of the ventricular activation for the narrow and NICD patients (emergence or extension of “blue” areas on the LV and peripacing activation conduction delays). In contrast, LBBB benefits from BVP by reduction of the LV activation delay (disappearance of “dark blue” area by collision of the RV and LV activation fronts).

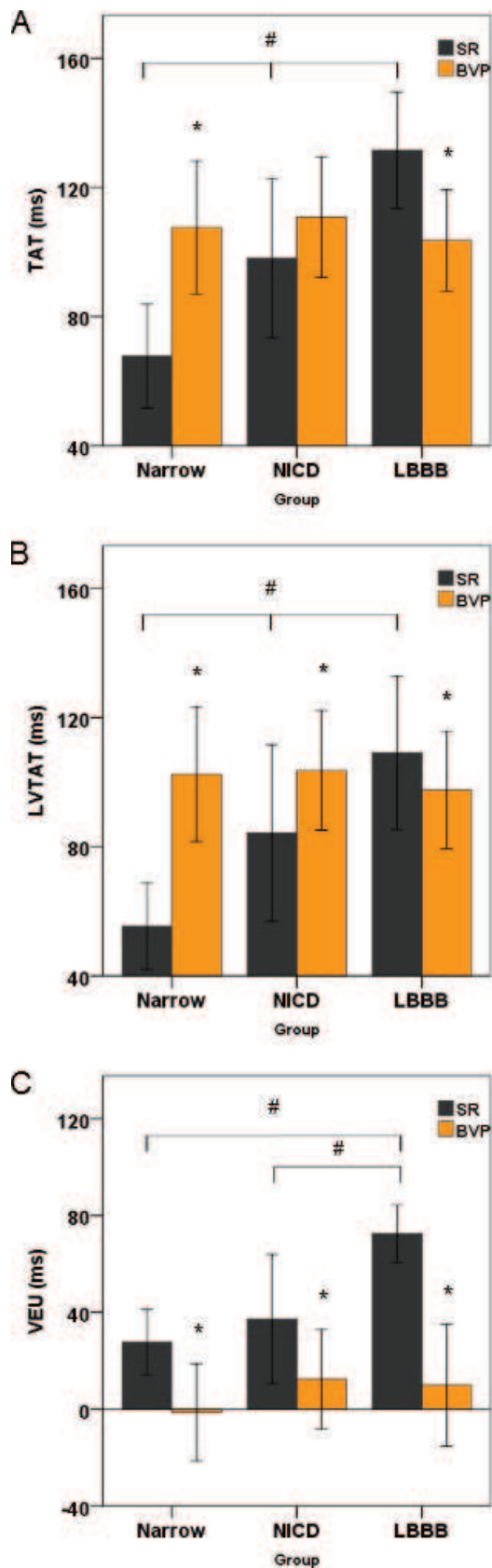


FIGURE 2

Comparison between the three groups of patients (narrow QRS duration “narrow”, NICD, LBBB) of the electrical dyssynchrony parameters TAT (A), LVTAT (B) and VEU (C) for both baseline (black bars, “SR”) and BVP (orange bars, “BVP”) activations. * means $p < 0.01$ for comparison between “SR” and “BVP”. # means $p < 0.001$ for overall comparison of “SR” values between the three groups and $p < 0.05$ (at least) for subsequent comparison within the three groups (except panel C between narrow and NICD). Overall comparison of “BVP” values between the three groups was statistically non-significant ($p > 0.05$). Error bars: $\pm 1SD$.

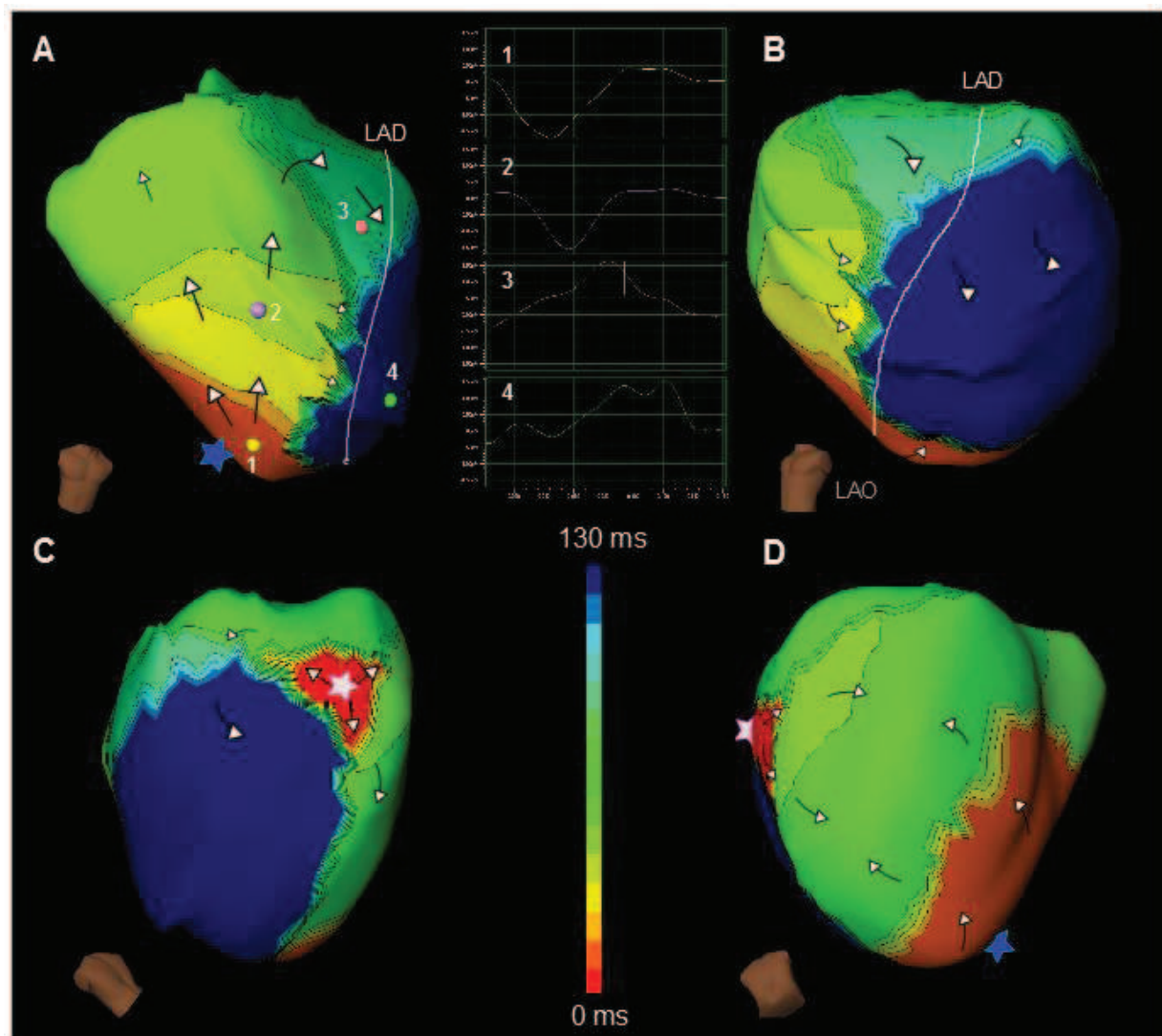


FIGURE 3:

Electrocardiographic maps of a NICD patient (same as figure 1) during BVP. Four different views are oriented as shown by the torso (there is overlap between adjacent views). LAO: left anterior oblique view. Blue stars indicate RV pacing location. White stars indicate LV pacing location. LAD: left anterior descending artery. Color dots are local electrograms and numbered from 1 to 4 (referred to map "A"). White arrows indicate the direction of the activation wave fronts. Thin black curves represent isochrones (every 9ms). A: starting from the pacing site, the activation spreads rapidly and radially to the RV. It is only at the level of the LAD projection (see "A") and at the posterior face of the LV (see "D") that the activation is

delayed (crowding of isochrones). Initial electrograms showed negative QRS complex (1, 2), while remote electrograms had positive QRS complex (3, 4). B: the anterior line of conduction delay prevents the activation wavefront from propagating to the LV in such a way that the anterior wall of the LV is activated from the base. C: isochronal activation crowding surrounds the LV pacing site delineating a primary area of activation. Beyond this ring of conduction delay, the activation velocity raises (spacing of isochrones, large unicolor area). D: merging of two activation fronts at the posterior face of the LV.

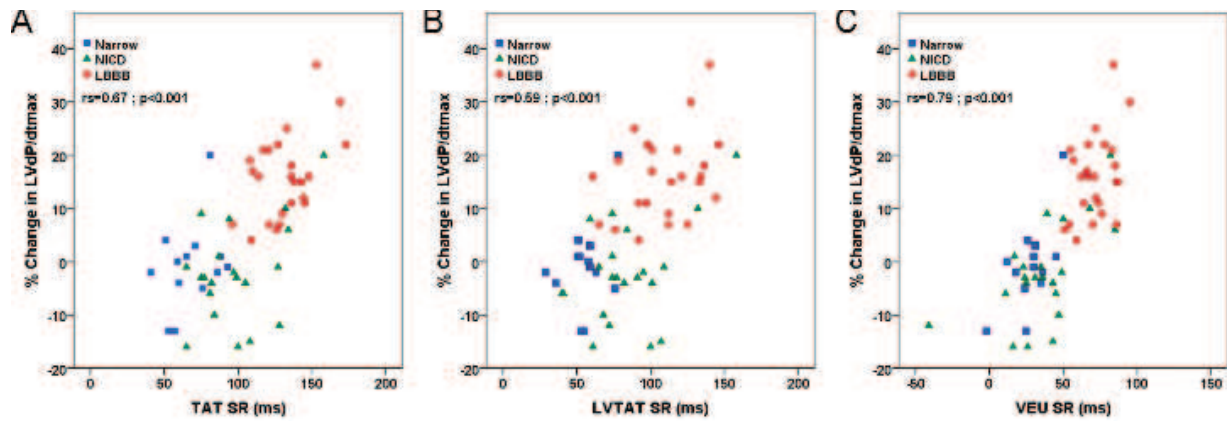


FIGURE 4:

Correlation between TAT_{SR} (A), LVTAT_{SR} (B), VEU_{SR} (C) and changes in LVdP/dt_{max} induced by BVP compared with baseline activation.

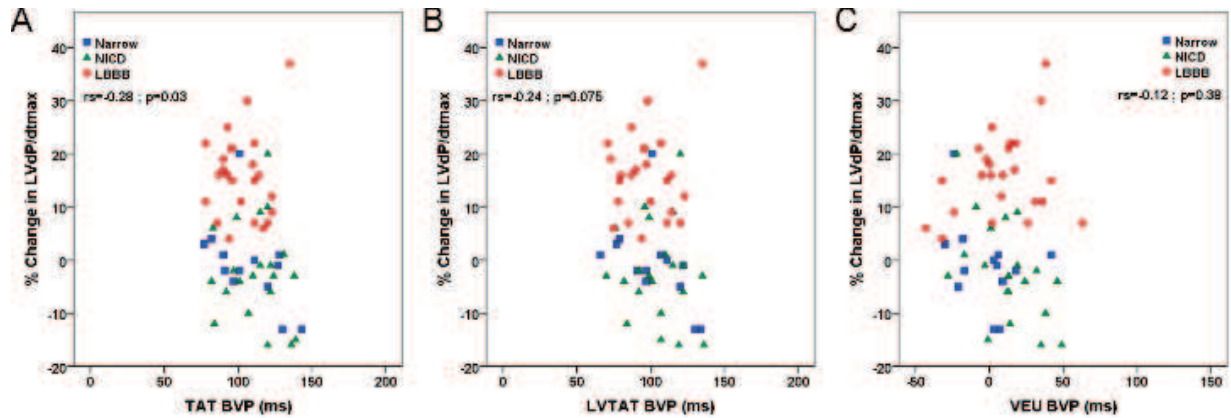


FIGURE 5:

Correlation between TAT_{BVP} (A), $LVTAT_{BVP}$ (B), VEU_{BVP} (C) and changes in $LVdP/dt_{max}$ induced by BVP compared with baseline activation. For comparison purpose we used the same scales as figure 4.

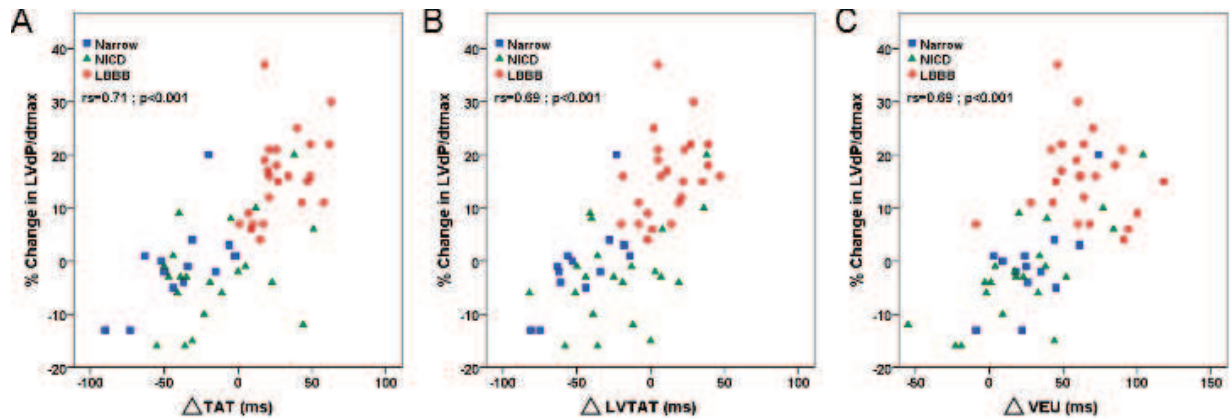


FIGURE 6:

Correlation between ΔTAT (A), $\Delta LVTAT$ (B), ΔVEU (C) and changes in $LVdP/dt_{max}$ induced by BVP compared with baseline activation.

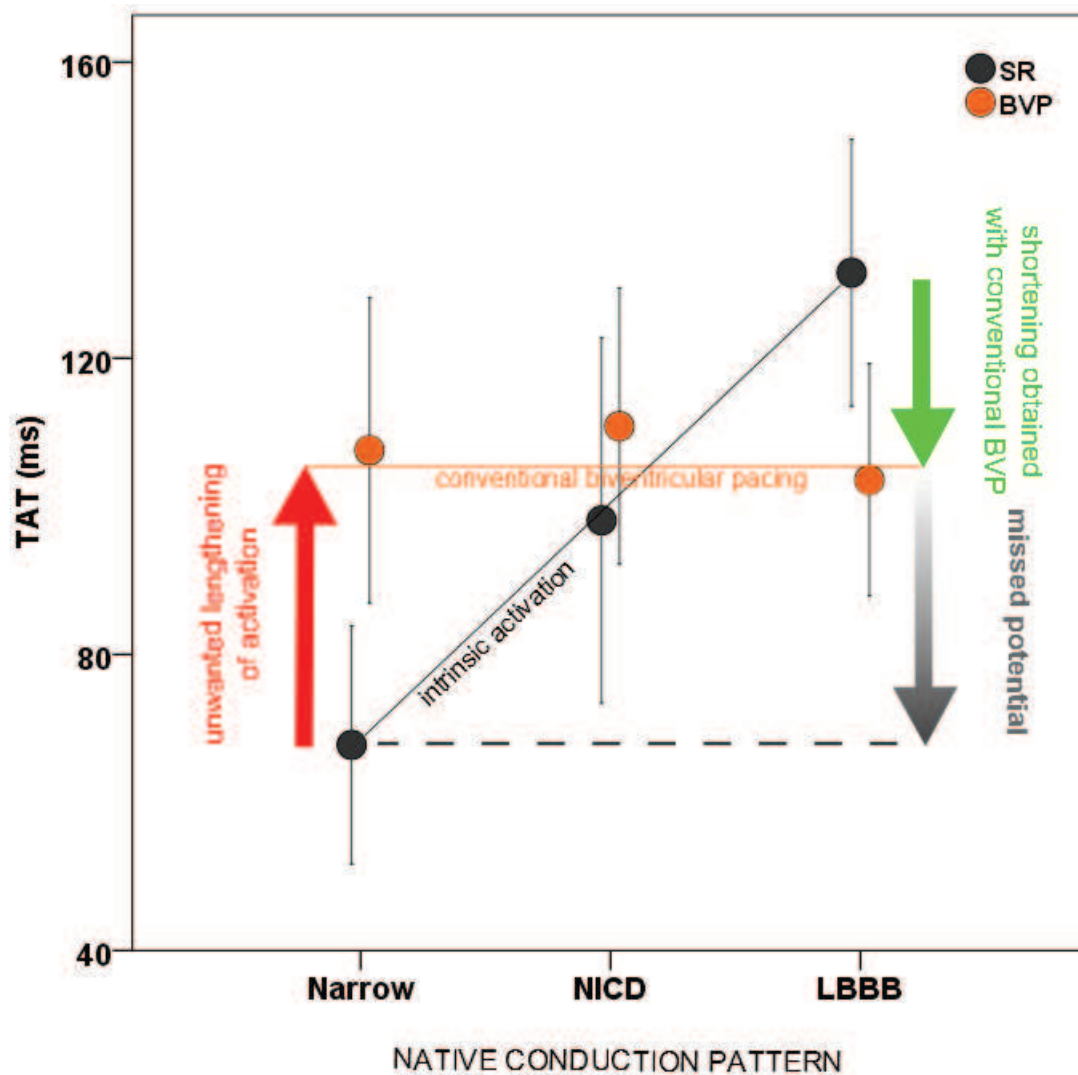


FIGURE 7:

The missed potential of conventional BVP. Figure derived from figure 2 panel A. Comparison between the three groups of patients (narrow QRS duration “narrow”, NICD, LBBB) of the TAT for both baseline (black dots, “SR”) and BVP (orange dots, “BVP”) activations. Error bars: ± 1 SD. Conventional BVP only reduces the TAT in severely dyssynchronous patients (green arrow) and creates/worsens electrical dyssynchrony (red arrow) when applied to patients with near normal conduction. The gap between the BVP performance in resynchronization (orange line) and the lower level of dyssynchrony observed (dotted line) represents the “missed potential” of conventional BVP (grey arrow).

11 EFFETS HEMODYNAMIQUES ET ELECTRIQUES DE LA STIMULATION VENTRICULAIRE GAUCHE MULTIPOINTS SUR UN MODELE CANIN DE BLOC DE BRANCHE GAUCHE.*

*Ploux S, Strik M, van Hunnik A, van Middendorp L, Kuiper M, Prinzen FW: Acute electrical and hemodynamic effects of multisite left ventricular pacing for cardiac resynchronization therapy in the dyssynchronous canine heart. *Heart Rhythm Off J Heart Rhythm Soc* 2013.⁶⁸

11.1 INTRODUCTION

Pour améliorer le pourcentage de réponse favorable à la resynchronisation, certains auteurs ont proposé une stimulation multipoints.⁶⁹⁻⁷² En effet, il n'est pas rare chez des patients resynchronisés de constater la persistance d'un asynchronisme ventriculaire.^{73,74} L'idée principe de la stimulation multipoints est d'augmenter le nombre de sites de stimulation afin de réduire le temps d'activation globale et de supprimer les zones d'activation retardée. Ce concept théorique se heurte toutefois 1) à une réalité pratique où le positionnement de plusieurs sondes est parfois difficile voire impossible 2) à l'absence de démonstration d'une efficacité hémodynamique et/ou clinique supérieure d'une stimulation multipoints par rapport à une stimulation BIV traditionnelle.

L'objectif principal de cette étude était donc d'évaluer, sur un modèle canin de bloc de branche gauche, l'impact hémodynamique et électrique d'une stimulation multipoints ventriculaires gauches (jusqu'à 7 sites de stimulation simultanés).

Ce travail a été réalisé dans le laboratoire du Professeur Prinzen à Maastricht, Pays Bas.

11.2 METHODE ET RESULTATS

Neuf chiens sans cardiopathie ont initialement bénéficié d'une ablation de la branche gauche. Quatre mois après cette intervention, une deuxième procédure était réalisée sous anesthésie générale avec 1) positionnement, d'un cathéter manomètre dans le ventricule droit et dans le ventricule gauche, d'un cathéter de conductance ventriculaire gauche et de 4 électrodes électrocardiographiques de surface 2) réalisation d'une thoracotomie avec mise en place de 2 bandes circonférentielles portant chacune deux rangées d'électrodes séparées de 1 cm ; une bande était cousue en regard de la base du cœur, l'autre de la partie médiane ; 2 électrodes additionnelles étaient cousues sur l'oreillette droite et à l'apex du ventricule gauche 3) 7 électrodes ventriculaires gauches de localisations prédéfinies sur les bandes (antéro-basale, latéro-basale, postéro-basale, antéro-médiane, latéro-médiane, postéro-médiane, et apicale) permettaient une stimulation ventriculaire gauche mono ou multipoints.

Les pressions et volumes cardiaques, l'électrocardiogramme et les cartes d'activation épicaudique de contact étaient recueillis durant chaque séquence de stimulation (mode DOO, délai AV fixe à 70 ms). Un premier site de stimulation (parmi les 7 sites prédéfinis) était sélectionné de façon aléatoire (stimulation mono-VG). Durant cette séquence de stimulation mono-VG, le système de cartographie de contact permettait d'identifier le site le plus retardé électriquement parmi les 6 autres sites prédéfinis. Cette seconde électrode était utilisée avec la première pour réaliser une stimulation bi-VG. Après chaque séquence, l'électrode présentant l'activation la plus retardée était associée pour permettre successivement une stimulation tri-VG, quadri-VG puis septuple-VG (stimulation simultanée avec toutes les électrodes).

Paramètres électriques : la stimulation mono-VG ne permettait pas de réduire le temps d'activation ventriculaire gauche (LVTAT) par rapport au bloc de branche gauche ; à l'opposé, la stimulation multi-VG permettait une réduction significative du LVTAT, l'amplitude de cette réduction dépendant du nombre d'électrodes : $-14.3 \pm 13\%$, $-22.9 \pm 11.5\%$, $-29.2 \pm 8.2\%$, et $-41.3 \pm 5\%$ pour les stimulations bi-VG, tri-VG, quadri-VG et septuple-VG respectivement ($p < 0.001$ pour la comparaison globale). La stimulation mono-VG ne modifiait pas significativement la dispersion de la repolarisation ; alors que l'augmentation successive du nombre d'électrodes de stimulation permettait d'améliorer ce paramètre : $-2.5 \pm 17.8\%$, $-6.3 \pm 17.4\%$, $-9.7 \pm 15.9\%$ et -

14.2±19.5% de réduction de la dispersion de repolarisation pour les stimulations bi-VG, tri-VG, quadri-VG et septuple-VG respectivement ($p<0.02$ pour la comparaison globale).

Paramètres hémodynamiques : une stimulation mono-VG était associée avec en moyenne une augmentation de la $dP/dt_{\max}VG$ de 10.7±7.7% par rapport à l'activation spontanée de l'animal. L'addition d'électrodes permettait une augmentation graduelle de la $dP/dt_{\max}VG$ pour atteindre 16.4±8.7% pour la configuration de stimulation réunissant les 7 électrodes ($p<0.001$ pour la comparaison globale).

Corrélation hémodynamique/temps d'activation : nous n'avons pas retrouvé de corrélation significative entre amélioration hémodynamique (% de changement de $dP/dt_{\max}VG$) et réduction d'asynchronisme VG (% de changement de LVTAT).

Site optimal versus stimulation multipoints : si l'on regroupe pour chaque expérimentation les deux sites prodiguant les meilleurs résultats hémodynamiques (groupe « best »), les deux sites associés aux plus mauvais résultats hémodynamiques (groupe « worst ») et les trois sites intermédiaires (« médium ») on constate que l'addition d'électrode ne bénéficie qu'aux groupes « worst » et « médium ». Ainsi, lorsque la stimulation mono-VG est d'emblée optimale, la stimulation multi-points n'apporte pas de bénéfice hémodynamique. En revanche, pour les trois même groupes, la réduction du temps d'activation suivait un profil similaire, proportionnel au nombre d'électrodes.

11.3 CONCLUSION

Il s'agit de la première expérimentation animale validant l'intérêt potentiel d'une véritable stimulation multipoints (> 2 ou 3 sites ventriculaires). Nous avons observé un bénéfice hémodynamique aigu significatif lors d'une stimulation multipoints suggérant une possible amélioration de la réponse après resynchronisation sans nécessité de recherche d'un éventuel site de stimulation optimal. L'augmentation successive du nombre d'électrodes est également associée avec une réduction parallèle du temps d'activation ventriculaire gauche. Cette réduction de l'asynchronisme électrique pourrait engendrer au long cours un remodelage inverse (génétique, moléculaire, cellulaire, tissulaire) supérieur à celui déjà observé lors d'une

stimulation BIV traditionnelle. La réduction de la dispersion de la repolarisation pourrait être associée au long cours avec un bénéfice en termes de prévention du risque rythmique et de la mort subite.

Les résultats favorables de cette étude animale pourrait justifier 1) d'une étude recherchant la validation d'une stimulation multipoints chez l'homme (possible étude hémodynamique aigue réalisée lors d'une intervention chirurgicale requérant une sternotomie) 2) d'un programme de recherche industriel visant à développer une voie d'abord et un dispositif permettant une stimulation multipoints.

Acute electrical and hemodynamic effects of multisite left ventricular pacing for cardiac resynchronization therapy in the dyssynchronous canine heart

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BACKGROUND Multisite left ventricular (multi-LV) epicardial pacing has been proposed as an alternative to conventional single-site LV (single-LV) pacing to increase the efficacy of cardiac resynchronization therapy.

OBJECTIVE To compare the effects of multi-LV versus single-LV pacing in dogs with left bundle branch block (LBBB).

METHODS Studies were performed in 9 anesthetized dogs with chronic LBBB using 7 LV epicardial electrodes. Each electrode was tested alone and in combination with 1, 2, 3, and 6 other electrodes, the sequence of which was chosen on the basis of practical real-time electrical mapping to determine the site of the latest activation. LV total activation time (LVTAT) and dispersion of repolarization (DRep) were measured by using approximately 100 electrodes around the ventricles. LV contractility was assessed as the maximum derivative of left ventricular pressure (LVdP/dt_{max}).

RESULTS Single-LV pacing provided, on average, a $-4.0\% \pm 9.3\%$ change in LVTAT and $0.2\% \pm 13.7\%$ change in DRep. Multi-LV pacing markedly decreased both LVTAT and DRep in a stepwise fashion to reach $-41.3\% \pm 5\%$ ($P < .001$ for overall comparison) and $-14.2\% \pm 19.5\%$ ($P < .02$ for overall comparison) in the septuple-LV pacing configuration, respectively. Single-LV pacing provided a mean increase of $10.7\% \pm 7.7\%$ in LVdP/dt_{max}.

LVdP/dt_{max} incrementally increased by the addition of pacing electrodes to $16.4\% \pm 8.7\%$ ($P < .001$ for overall comparison). High response to single-LV pacing could not be improved further during multi-LV pacing.

CONCLUSIONS Compared with single-LV pacing, multi-LV pacing can considerably reduce both LVTAT and DRep in dogs with LBBB, but the improvement in contractility is limited to conditions where single-LV pacing provides suboptimal improvement. Further studies are warranted to determine whether these acute effects translate in antiarrhythmic properties and better long-term outcomes.

KEYWORDS Cardiac resynchronization therapy; Multisite left ventricular pacing; Heart failure; Left bundle branch block; Cardiac mapping; Biventricular pacing

ABBREVIATIONS CRT = cardiac resynchronization therapy; DRep = dispersion of repolarization; LBBB = left bundle branch block; LV = left ventricular; LVdP/dt_{max} = maximum derivative of left ventricular pressure; LVTAT = left ventricular total activation time; multi-LV = multisite left ventricular; RV = right ventricular; single-LV = single-site left ventricular

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Introduction

Cardiac resynchronization therapy (CRT) is an established treatment of patients with symptomatic heart failure, severely impaired left ventricular (LV) function, and conduction

disorders, most often in the form of left bundle branch block (LBBB). Large randomized trials have demonstrated that CRT improves quality of life and symptoms as well as reduces heart failure–related hospitalizations and mortality. However, approximately one-third of the patients appear not to respond significantly to CRT.¹ Because CRT is a relatively expensive and invasive technique, requiring virtually irreversible device implantation, there is considerable interest in attempts to improve the response rate. While most attention has been focused on criteria for patient selection, an at least equally important approach is to improve therapy delivery. As the benefits of CRT are particularly thought to result from improved electrical resynchronization of the LV, multi-site LV pacing has arisen as an alternative strategy for improving the success rate of CRT. However, thus far this

Dr Ploux received a grant from la Fédération Française de Cardiologie. He was supported by the French government's l'Agence Nationale de la Recherche au titre du programme Investissements d'Avenir (reference no. ANR-10-IAHU-04). This research was performed within the framework of the Center for Translational Molecular Medicine (www.ctmm.nl), project COHFAR (grant no. 01C-203), and supported by the Dutch Heart Foundation. Dr Prinzen has received research grants from Medtronic, EBR Systems, Proteus Biomedical, Biological Delivery Systems, and MSD. **Address reprint requests and correspondence:** Dr Sylvain Ploux, Hôpital de Haut-Lévêque, CHU de Bordeaux, Avenue de Magellan, 33604 Pessac, France. E-mail address: sylvain.ploux@free.fr.

question has not been specifically addressed. Human data are restricted to LV pacing at 2 sites (triventricular pacing), and acute hemodynamic studies evaluating the role of triventricular pacing have shown conflicting results.²⁻⁵

The hypothesis of the present study was that both electrical resynchronization and hemodynamic function improve with an increasing number of LV pacing sites. In order to investigate this hypothesis, experiments were performed in dogs with chronic LBBB.⁶ In this well-established animal model of dyssynchrony, we pursued optimal resynchronization by using near real-time electrical mapping to locate and stimulate the latest activation of 7 predetermined LV pacing electrodes: first 1 and then 2, 3, 4, and all 7 electrodes simultaneously. This design allowed an extensive comparison of many pacing sites and invasive hemodynamic measurements.

Methods

Animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. The protocol was approved by the Animal Experimental Committee of Maastricht University.

Experimental setup

The experiments were performed on 9 adult mongrel dogs of either sex and unknown age, weighing 22.0 ± 0.5 kg. After the induction of Pentothal, anesthesia was maintained by the infusion of midazolam (0.25 mg/(kg · h) intravenously) and sufentanil (3 µg/(kg · h) intravenously). LBBB was created by radiofrequency ablation 16 weeks before the acute experiment, allowing for ventricular remodeling to occur.

Surface electrocardiograms were recorded from the limb lead electrodes. LV pressure and volume were measured by using a combination of 7-F catheter-tip manometer and

conductance catheter, and right ventricular (RV) pressure measured by using a 7-F catheter-tip manometer (CD-Leycom, Zoetermeer, The Netherlands). These catheters were introduced into the carotid artery and jugular vein, respectively. After thoracotomy, 2 multielectrode bands for recording and pacing were positioned around the heart, one approximately 1 cm below the base and the other around the mid-level. Each of these customized bands contained 2 rows of electrodes (2×30 and 2×22 , respectively), approximately 1 cm apart. To measure the electrical activation of the septum, an 8-pole multielectrode catheter (Daig Livewire TC, Minnetonka, MN) was placed through the jugular vein in contact with the RV septum.

Temporary myocardial pacing leads (Medtronic, type 6500, Minneapolis, MN) were sutured to the epicardial surface of the roof of the right atrium and to the LV apex. Seven predefined epicardial electrodes were used for the LV pacing protocol: at the anterior, lateral, and posterior walls of both the basal and the mid-level of the LV (from the bands) and at the LV apex (lead).

After instrumentation and hemodynamic stabilization, electrical mapping and hemodynamic measurements were acquired simultaneously. For all 7 epicardial electrodes, the pacing threshold was determined. Each LV electrode was first used for single-LV pacing, the order of which was randomized per dog. Subsequently, a second LV electrode was added, being the 1 of the 6 remaining with the longest activation time (located in the latest activated region) during single-LV pacing, as assessed by epicardial mapping (Figure 1). The same procedure was repeated for the third and the fourth LV electrode (Figure 1). Finally, all 7 LV electrodes were paced together (5 and 6 electrodes together were not tested). The ventricular pacing mode was DOO, 10 beats/min above the sinus rhythm. Baseline atrial pacing measurements were repeated at each pacing site in the AOO mode at the same rate. The paced AV interval was set at 70 ms, and full capture was confirmed by cardiac mapping

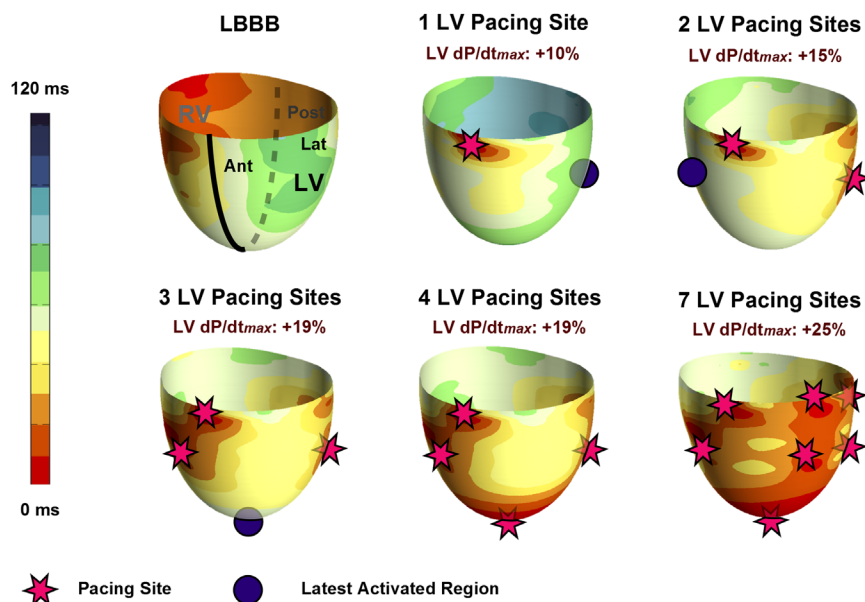


Figure 1 Overview of the pacing protocol. Three-dimensional epicardial activation maps of both ventricles during LBBB activation and single-, dual-, triple-, quadruple-, and septuple-LV pacing configurations in the same dog. In this example, single-LV pacing started with the basal-anterior LV electrode (center panel, top row). During single-LV pacing, the latest remaining electrode was middle-posterior (blue dot) and was thereby used for the dual LV-pacing configuration (right panel, top row). Each time the latest activated electrode was added to achieve triple and quadruple-LV pacing (bottom row, left and middle maps). Finally, the 7 electrodes were paced together. LBBB = left bundle branch block; LV = left ventricular; LVdP/dt_{max} = maximum derivative of left ventricular pressure; single-LV = single-site left ventricular.

(absence of early activation at the level of the RV septum). The ventricular electrodes used for multisite left ventricular (multi-LV) pacing were paced simultaneously. The recording of measurements started 30 seconds after the initiation of pacing to achieve hemodynamic stability. Data were then acquired for 20 seconds to include 4 respiratory cycles.

Data analysis

Data analysis was performed by using custom MATLAB software (MathWorks, Natick, MA). From the LV and RV pressure signals, the following parameters were derived: systolic and end-diastolic pressure, maximum and minimum derivatives of the ventricular pressure (dp/dt_{\max} , dp/dt_{\min}). LV volume was determined from the conductance data recorded with a Leycom Sigma 5DF signal conditioner processor (CD Leycom, Zoetermeer, The Netherlands). For all cardiac mapping electrodes, activation times were calculated as the time difference between the onset of the Q wave (during baseline LBBB) or pacing artifact (during ventricular pacing) and the time of steepest negative deflection in the depolarization part of the electrogram. LV total activation time (LVTAT) was calculated as the maximal difference in activation time between all LV electrodes. Repolarization times were estimated as the time difference between the onset of the Q wave or pacing artifact and the time of steepest positive deflection in the repolarization part of the electrogram. The total dispersion of repolarization (DRep) was quantified as the maximum time difference in repolarization from the electrode bands.⁷

Statistical analysis

Statistical analyses were performed by using the SPSS software (version 18.0, SPSS Inc, Chicago, IL). All values are presented as mean \pm SD (mean \pm standard error for Figure 5). For all pacing conditions, the hemodynamic or electrical results are expressed as a percentage of the corresponding baseline. Changes in hemodynamics and electrical parameters were compared among the different pacing configurations by using repeated measures analysis of variance. The Greenhouse-Geisser correction was applied in the case of violation of the sphericity assumption. Bonferroni correction was used for post hoc comparisons. The relationship between $LVdp/dt_{\max}$ and LVTAT changes was assessed by using the Pearson (for normally distributed data) or the Spearman correlation coefficients. Statistical significance was assumed at $P < .05$.

Results

Effects of multi-LV pacing on electrical activation/repolarization

In each of the 9 experiments, single-, dual-, triple-, and quadruple-LV pacing configurations were tested at each of the 7 LV segments except for 1 dog that had partly missing data for both triple- and quadruple-LV pacing. Neither single-LV pacing nor multi-LV pacing induced ventricular arrhythmias even when 7 sites were stimulated at an output up to 10 V.

Figure 1 shows electrical maps during baseline (LBBB) and during LV pacing at an incremental amount of simultaneously stimulated electrodes. In this example, single-site anterobasal LV pacing did not resynchronize the LV as the area of latest activation shifted from the LV lateral wall (during LBBB) toward the midposterior region with even increased electrical asynchrony (evidenced by the dark-blue color contour). Simultaneously stimulating the second LV electrode closest to the midposterior region eradicated the area of delayed activation and clearly resynchronized the LV. Adding more pacing sites further resynchronized the LV, as areas of the latest activation were selected to undergo stimulation simultaneously with the electrodes selected in previous settings.

On average, single-LV pacing did not change LVTAT as compared with intrinsic LV activation (AAI pacing) in the LBBB hearts ($-4.0\% \pm 9.3\%$; $P > .9$). LVTAT was even increased by $\geq 5\%$ in 13 of the 61 tested single-LV pacing sites (21%) and by $\geq 10\%$ in 5 of the 61 single-LV pacing sites (8%). In contrast, multi-LV pacing markedly and significantly decreased the LVTAT in a stepwise manner: $-14.3\% \pm 13\%$, $-22.9\% \pm 11.5\%$, $-29.2\% \pm 8.2\%$, and $-41.3\% \pm 5\%$ for dual-, triple-, quadruple-, and septuple-LV pacing, respectively ($P \leq .001$ for differences among all pacing configurations; Figure 2). Table 1 gives absolute values for electrocardiographic and hemodynamic parameters for all pacing modes where similar reductions were observed for QRS duration and total activation time. These reductions in total activation times were observed consistently in all experiments.

Single-LV pacing yielded a nonsignificant change of $0.2\% \pm 13.7\%$ in DRep (as compared with baseline LBBB; $P = .9$). Adding more pacing sites progressively decreased DRep: $-2.5\% \pm 17.8\%$, $-6.3\% \pm 17.4\%$, $-9.7\% \pm 15.9\%$, and $-14.2\% \pm 19.5\%$ for dual-, triple-, quadruple-, and septuple-LV pacing, respectively ($P \leq .02$ for differences among all pacing configurations; Figure 3). The corrected QT duration was reduced similarly (Table 1).

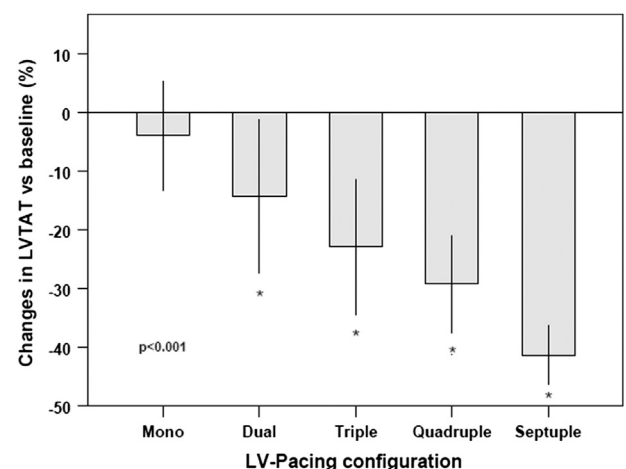


Figure 2 Percent changes in LVTAT during single-, dual-, triple-, quadruple-, and septuple-LV pacing compared with baseline atrial pacing in the LBBB heart. All values are presented as mean \pm SD. $P \leq .001$ for differences among all pacing configurations. * $P \leq .01$ vs single-LV pacing. LV = left ventricular; LVTAT = left ventricular total activation time.

Table 1 Electrophysiological and hemodynamic characteristics during baseline atrial pacing (LBBB) and single-, dual-, triple-, quadruple-, and septuple-LV pacing

	LBBB	Single	Dual	Triple	Quadruple	Septuple
Electrophysiological parameters						
Heart rate (beats/min)	141 ± 14	141 ± 14	142 ± 13	141 ± 13	141 ± 14	143 ± 14
PR time (ms)	132 ± 21	73 ± 10*	73 ± 11*	75 ± 10*	74 ± 10*	75 ± 10*
QRS duration (ms)	109 ± 9	113 ± 10	104 ± 12†	98 ± 10*†	95 ± 10*†	89 ± 9*†
Corrected QT duration (ms)	350 ± 21	362 ± 22	354 ± 24†	347 ± 22†	344 ± 22†	342 ± 27†
Total activation time (ms)	91 ± 11	95 ± 9	85 ± 10†	80 ± 11†	77 ± 10†	73 ± 9*†
LV total activation time (ms)	91 ± 11	88 ± 6	78 ± 9†	70 ± 9*†	64 ± 5*†	53 ± 4*†
Dispersion repolarization (ms)	90 ± 14	89 ± 9	86 ± 11	83 ± 12	80 ± 11†	76 ± 15
Hemodynamic parameters						
LV Pmax (mm Hg)	83 ± 10	83 ± 10	83 ± 10	84 ± 10	84 ± 10	84 ± 10
LVdP/dt _{max} (mm Hg/s)	1325 ± 346	1478 ± 459	1514 ± 465	1524 ± 473	1529 ± 486	1542 ± 496
LVdP/dt _{min} (mm Hg/s)	-1440 ± 356	-1373 ± 355	-1395 ± 368	-1394 ± 355	-1389 ± 356	-1350 ± 358
LV EDP (mm Hg)	10 ± 6	8 ± 5	8 ± 5	8 ± 5	8 ± 5	9 ± 5
SV (mL)	22 ± 09	26 ± 12	26 ± 11	27 ± 11	27 ± 11	28 ± 12
RV Pmax (mm Hg)	37 ± 8	33 ± 8	33 ± 8	33 ± 8	33 ± 8	34 ± 9
RVdP/dt _{max} (mm Hg/s)	612 ± 148	622 ± 250	613 ± 205	638 ± 279	608 ± 255	597 ± 222
RVdP/dt _{min} (mm Hg/s)	-417 ± 115	-379 ± 108	-386 ± 110	-387 ± 106	-392 ± 108	-392 ± 107
RV EDP (mm Hg)	8 ± 7	7 ± 6	8 ± 6	8 ± 7	8 ± 7	8 ± 7

All values are presented as mean ± SD. All *P* values are based on the general linear model for repeated measures.

dP/dt_{max} = maximum derivative of the corresponding ventricular pressure; dP/dt_{min} = minimum derivative of the corresponding ventricular pressure; EDP = end-diastolic pressure; LV = left ventricular; Pmax = peak systolic pressure; RV = right ventricular; SV = stroke volume.

**P* < .05 for comparison with LBBB.

†*P* < .05 for comparison with single LV pacing.

Effects of multi-LV pacing on hemodynamic performance

Single-LV pacing provided a mean increase of 10.7% ± 7.7% in LVdP/dt_{max} (*P* = .04), with the optimal single-LV pacing site being dog specific. On average, pacing the anterior, lateral, and posterior base increased LVdP/dt_{max} by 6.6% ± 6.9%, 9.2% ± 10.0%, and 12.9% ± 7.9%, respectively. Pacing the anterior, lateral, and posterior faces of the LV middle segment yielded 14.3% ± 9.4%, 9.8% ± 7.9%, and 8.5% ± 13.0% increase in LVdP/dt_{max}, respectively, while the apex was associated with a mean increase of

14.1% ± 7.8% (*P* = .024 for comparison between the 7 locations). The anterior and lateral bases were found to be the worst site 3 and 2 times, respectively; the posterior bases were the best site in 2 dogs, the mid-anterior region was the best in 2 cases, and the worst in 1; the mid-lateral region was the best in 1 dog and the worst in another; the mid-posterior region was the best in 2 dogs and the worst in 2 others; the apex was the best site in 2 dogs.

Adding more pacing sites provided a gradual increase in LVdP/dt_{max}, reaching 16.4% ± 8.7% for the septuple configuration (*P* ≤ .001 for differences among all pacing configurations; Figure 4). Unlike the electrical changes for which we observed a fairly consistent step-by-step decrease in each dog, the hemodynamic response to multi-LV pacing was variable from one experiment to another (some dogs were more sensitive to multi-LV pacing than others). Correlations between LVdP/dt_{max} and LVTAT changes from the different pacing configurations are presented in Table 2 for each dog: a modestly significant correlation was found in 3 dogs, and no correlation was found in the remaining 6 dogs. These significant correlation coefficients were observed for those dogs that benefited most from multi-LV pacing (their progressive hemodynamic improvement matched with the progressive decrease in LVTAT induced by the addition of pacing sites).

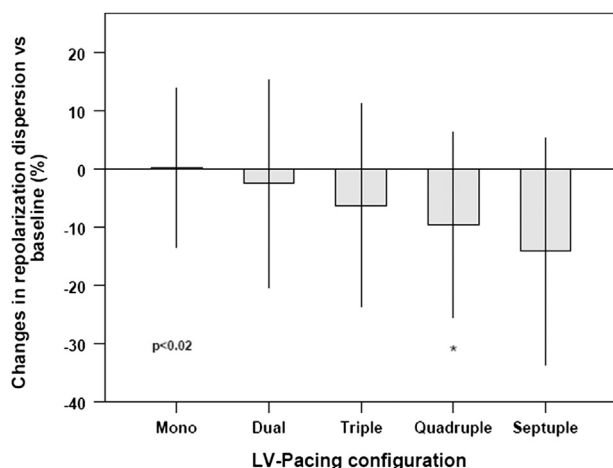


Figure 3 Percent changes in the dispersion of repolarization during single-, dual-, triple-, quadruple-, and septuple-LV pacing compared with baseline atrial pacing in the LBBB heart. All values are presented as mean ± SD. *P* < .02 for differences among all pacing configurations. **P* ≤ .03 vs single-LV pacing. LV = left ventricular; single-LV = single-site left ventricular.

Effect of multi-LV pacing according to the single-LV pacing effect

Figure 5A (left panel) shows the hemodynamic responses on the different multi-LV configurations, distinguishing between scenarios with the 2 single-LV sites that, within

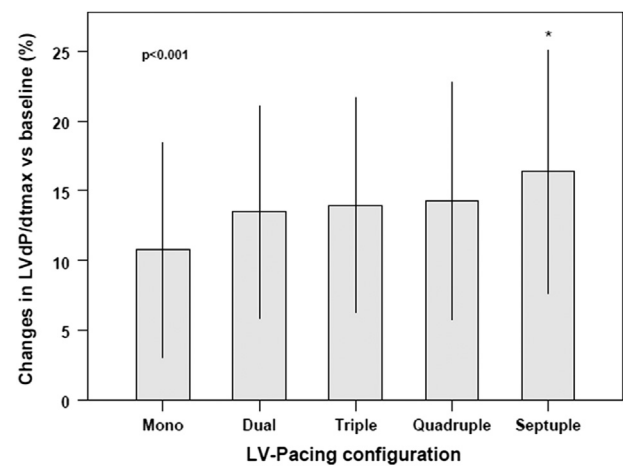


Figure 4 Percent changes in LVdP/dt_{max} during single-, dual-, triple-, quadruple-, and septuple-LV pacing compared with baseline atrial pacing in the LBBB heart. All values are presented as mean ± SD. *P* ≤ .001 for differences among all pacing configurations. **P* ≤ .03 vs single-LV pacing. LBBB = left bundle branch block; LV = left ventricular; LVdP/dt_{max} = maximum derivative of left ventricular pressure.

each experiment, provided the largest increase in LVdP/dt_{max} (“best” sites), the 2 “worst” sites, and the 3 sites that yielded intermediate hemodynamic improvement (“medium” sites). When a single-LV pacing site provided a poor (worst) or intermediate (medium) hemodynamic response, adding more electrodes resulted in additional improvement. When the hemodynamic response was optimal (best) with a single-LV pacing site, no further improvement occurred with the addition of pacing site(s). Noteworthy, the pacing location during single-LV pacing was highly variable among the 3 groups whereas the mean local activation times in sinus rhythm were similar: 65 ± 22, 63 ± 21, and 70 ± 48 ms for the best, intermediate, and worst group, respectively (*P* = .7).

Figure 5B (right panel) shows the LVTAT changes for the same groups as defined above. The 3 groups differed by their effects on LVTAT induced by single-LV pacing but showed similar electrical behavior (LVTAT reduction) to multi-LV pacing.

Discussion

In the present animal study, we investigated a strategy for optimal delivery of CRT using real-time mapping and adding pacing sites at the latest activated regions. This study demonstrated that compared to single-LV pacing, multi-LV epicardial pacing produced faster ventricular electrical depolarization and repolarization and some additional improvement in systolic LV pump function. While the electrophysiological effects were clearly proportional to the number of pacing sites, the hemodynamic improvement was poorly correlated to the reduction in LVTAT. Multi-LV pacing caused only a significant improvement in hemodynamic response if pacing at a single-LV site provided suboptimal response.

Electrical changes induced by multi-LV pacing

LV pacing can improve the pump function of hearts with depressed ejection fraction and LBBB. In LBBB, the loss of

fast LV activation through the specialized conduction system leads to delayed and prolonged LV activation. Single-LV pacing does not reduce LVTAT. Single-LV pacing essentially results in a new stage of dyssynchrony, sometimes greater than the intrinsic conduction (Figure 1, top middle map). Conversely, multi-LV pacing can reduce it consistently and proportionally to the number of electrodes used, reaching a maximal reduction of approximately 41% in LVTAT. In fact, total and LV activation time as well as QRS duration approach near-physiological values.⁸ This reduction is larger than that reported in dogs with normal atrioventricular conduction (25% QRS width reduction with multi-LV pacing using 4 electrodes as compared with single-LV apex pacing).⁹ Similarly, in patients with heart failure, dual-LV pacing shortened QRS duration by 22% whereas single-site posterior base and lateral LV wall pacing increased it significantly by 2% and 12%.⁴ In our study, the reduction in LVTAT coincided with a reduction in DRep, a combination that may confer antiarrhythmic properties.¹⁰ Multi-LV pacing has been suggested as a method for reducing the possibility of reentry on the basis of the premise that synchronous activation of the heart should reduce the dispersion of the recovery of excitability.^{11,12}

Hemodynamic effect of multi-LV pacing

Overall, multi-LV pacing also provided a significant increase in LVdP/dt_{max} over single-LV pacing. However, the relationship between reduction in LVTAT and a hemodynamic benefit is not straightforward. There hardly exists a correlation between changes in LVTAT and LVdP/dt_{max}. This lack of correlation shows that the hemodynamic benefit of multi-LV pacing does not exclusively hinge on the degree of absolute electrical asynchrony. The present study demonstrates, in agreement with earlier studies, that the site of LV pacing is a primary determinant of the hemodynamic response to CRT, even though the physiological process by which 1 site surpasses another are not well understood.^{9,13} Furthermore, it is unknown what the effects of the interaction between an “optimal” and a “suboptimal” LV pacing spot are. In this study, the addition of electrodes was beneficial as long as the hemodynamic improvement was suboptimal.

Table 2 Relationship between changes in LVdP/dt_{max} and changes in LVTAT

Dog no.	Correlation		
	n	r	P
1	28	−.04	.8
2	14	.06	.8
3	28	−.36	.06
4	28	.06	.8
5	27	−.40	.04
6	27	−.50	<.01
7	28	−.29	.1
8	28	−.10	.6
9	27	−.41	.03

LVdP/dt_{max} = maximum derivative of left ventricular pressure; LVTAT = left ventricular total activation time; n = number of points.

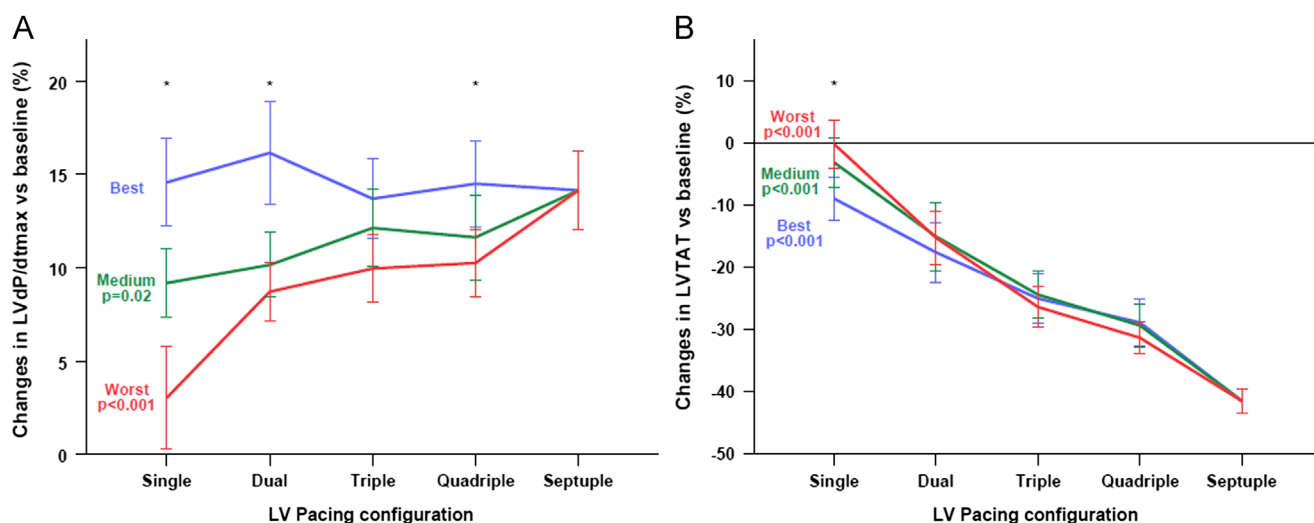


Figure 5 A: Percent increase in LVdP/dt_{max} versus baseline during single-, dual-, triple-, quadruple-, and septuple-LV pacing according to the hemodynamic improvement provided by single-LV pacing (7 modalities for each dog; n = 8). In blue: pooled data for the 2 best hemodynamic single-LV pacing (“best”; no significant differences between the different pacing configurations). In red: pooled data for the 2 worst hemodynamic single-LV pacing (“worst”; $P < .001$ for differences among all pacing configurations). In green: pooled data for the 3 remaining single-LV pacing, thus providing intermediate results (“medium”; $P < .02$ for differences among all pacing configurations). All values are presented as mean \pm standard error. $^*P \leq .05$ for differences among the 3 groups (best, medium, and worst) for the corresponding pacing configuration. B: Corresponding percent decrease in LVTAT versus baseline during single-, dual-, triple-, quadruple-, and septuple-LV pacing for the 3 groups (best, medium, and worst). All values are presented as mean \pm standard error. $^*P = .01$ for differences among the 3 groups (best, medium, and worst) for the corresponding pacing configuration. LV = left ventricular; LVTAT = left ventricular total activation time; LVdP/dt_{max} = maximum derivative of left ventricular pressure; single-LV = single-site left ventricular.

Conversely, when a large LVdP/dt_{max} increase was achieved (even with a single electrode), the addition of pacing sites was not detrimental. Figure 5B shows that single-LV pacing was able to provide similar hemodynamic response as multi-LV pacing despite different levels of LV resynchronization. It also shows that the hemodynamic course of the 3 groups of sites (best, medium, and worst) in response to multi-LV pacing strictly differed despite similar LVTAT reduction. These observations suggest that the hemodynamic improvement of a given pacing configuration is mostly driven by the best of the pacing electrodes used and may explain why, on average, dual-LV is better than single-LV pacing, triple-LV is better than dual-LV pacing, and so on: the likelihood of getting a favorable pacing site in the pacing set increases with the number of electrodes used. Our findings are supported by an acute hemodynamic study in 12 patients with heart failure, where the benefit of biventricular pacing using 2 LV leads was not superior to conventional biventricular pacing by using the best of 2 LV leads with an optimized AV delay.⁵

Human experience of multi-LV pacing is restricted to biventricular pacing using 1 RV and 2 LV leads (triventricular pacing). Two randomized trials with a small sample size have shown triventricular pacing to be associated with a higher reduction in LV end-systolic volume than conventional biventricular pacing, while the 6-minute walk distance did not significantly differ between the 2 groups.^{2,14} In these studies, only 1 biventricular configuration (out of 2) was tested against triventricular pacing. Bordachar et al¹⁵ compared triventricular pacing (1 RV + 2 LV electrodes) with conventional biventricular pacing in dogs with ischemic

heart failure and LBBB and did not find any significant difference between the 2 pacing modes. Differences between this canine study and ours are that we studied LV pacing instead of biventricular pacing, that we extended the concept of multi-LV pacing to 7 LV electrodes, and that additional pacing sites were chosen on the basis of near real-time electrical mapping, thus providing the best possible scenario for reducing electrical asynchrony.

Clinical implications

This study holds 2 possible clinical implications. First, multi-LV pacing appears to be effective in maximizing the hemodynamic benefit without requiring any optimization of the pacing site. Also interesting is the potential effect in preventing ventricular arrhythmias. Indeed, single-LV pacing has been suspected to be proarrhythmic with an increase in transmural heterogeneity of repolarization intrinsic to ventricular myocardium.¹⁶ Sudden death may occur in patients with heart failure even when implanted with an ICD. Shock delivery has been proven to be associated with death. Therefore, any strategy that prevents the occurrence of ventricular arrhythmias is welcome.¹⁷

Multi-LV pacing is nowadays restricted to triventricular pacing owing to technical limitations. The accumulation of pacing leads has evident limitation transvenously as well as pericardially. The current devices provide only 2 ventricular ports; adding ports will drain the battery and capacity would be too low to chronically supply more than 3 ventricular exits. In the light of the foregoing results, research in the development of dedicated materials may be considered. In

that respect, multielectrode leads and wireless pacing systems may offer potential advantages.

Experimental model and limitations

The present study was performed in the established model of experimental LBBB in the canine heart. Even in the absence of other heart disease, chronic LBBB leads to ventricular dilation and asymmetric hypertrophy and decrease in $LVdP/dt_{max}$.⁶ Results from this model have been shown to translate well to the clinical situation.¹⁸ Our heart segmentation is a simplification of the 17-segment AHA model to allow proper discrimination of the activation times of 7 electrodes.⁷ CRT was achieved by pure LV pacing, which has been proven to be as effective as biventricular pacing even at short AV delay.^{19,20} A pure assessment of different LV pacing configurations was ensured by using a short AV delay, which differs from the clinical practice where fusion with the intrinsic activation is sought. RV pacing was not considered because its participation to the LV activation during biventricular pacing (through the septum) has been found to be limited in dogs; therefore, the LV pacing approach provides the most sensitive scenario to test the hypothesis that reduction in electrical activation leads to improvements in pump function.²¹ As previously described, we observed a variation in the optimal pacing site between dogs.¹³ One may hypothesize that (1) the level of the LBB ablation was different between the dogs, with different degrees of septal lesion; (2) the remodeling process induced by the LBB ablation had individual variation; (3) the position of the atrial (which could modify the AV delay) and ventricular leads may have slightly varied, and (4) measurement variability could account for this result.

A particular aspect of the present study was the strategy aiming to deliver the best possible electrical resynchronization by using near real-time electrical mapping for finding the latest activated region at each step in the protocol.

Our results should be extrapolated to the human situation with caution because most of the CRT candidates have additional systolic impairment due to the underlying cardiomyopathy with possible areas of scar. We demonstrated a reduction of the total epicardial DRep by multi-LV pacing but the effect on the transmural DRep was not assessed. Also, this study was conducted in isolated proximal LBBB and results for other conduction defects are not warranted. Finally, acute hemodynamic improvement may not predict chronic outcome.²²

Conclusions

In dogs with chronic LBBB, multi-LV pacing reduces asynchrony of electrical activation and DRep compared to single-LV pacing. Reduction in LVTAT is probably not the mechanism by which multi-LV pacing improves the LV hemodynamic since its effect was similar to that observed for the best single-LV pacing site. Multi-LV pacing was particularly effective in improving suboptimal combination of pacing sites. Potential antiarrhythmic properties and

superiority in terms of LV reverse remodeling have to be specifically investigated in long-term studies.

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12 ETUDE COMPARATIVE DES MODES DE STIMULATION MONO-VG ET BIV SUR DIFFERENTS MODELES D'INSUFFISANCE CARDIAQUE AVEC BBG.*

*Lumens J, Ploux S, Strik M, et al. Comparative electromechanical and hemodynamic effects of left ventricular and biventricular pacing in dyssynchronous heart failure: electrical resynchronization versus left-right ventricular interaction. J Am Coll Cardiol 2013.⁷⁵

12.1 INTRODUCTION

La thérapie de resynchronisation cardiaque par stimulation BIV, comme son nom l'indique, a été initialement basée sur le concept d'une réduction des différents niveaux d'asynchronisme (atrio-ventriculaire, inter-ventriculaire et intra-ventriculaire) permettant un bénéfice hémodynamique et clinique, un remodelage inverse et une réduction de la mortalité. La diminution des temps d'activation ventriculaire est donc traditionnellement considérée comme un préalable au bénéfice survenant après cette thérapie. L'efficacité démontrée de la stimulation mono-VG équivalente à la stimulation BIV remet en cause cette théorie. En effet, il paraît improbable que l'influx naissant d'un site de stimulation épicaudique ventriculaire gauche isolé engendre une séquence d'activation ventriculaire « synchrone » ou plus rapide que celle observée en rythme spontané. Il paraît donc nécessaire de rechercher d'autres mécanismes impliqués dans le bénéfice observé après stimulation ventriculaire gauche. Les modèles de simulation informatique complémentaires aux modèles animaux et cliniques permettent d'appréhender l'interaction complexe entre mécanique et électricité, relation centrale dans la compréhension des mécanismes impliqués dans les bénéfices associés à la resynchronisation.

Les objectifs de cette étude étaient :

- 1) de combiner données d'expérimentation animale, d'expérimentation clinique et de modélisation informatique pour comparer stimulation mono-VG et stimulation BIV dans le cadre d'une insuffisance cardiaque avec BBG.

- 2) de définir les mécanismes physiopathologiques impliqués dans le bénéfice hémodynamique respectivement apporté par la stimulation mono-VG et la stimulation BIV.

12.2 METHODE ET RESULTATS

Etude animale : différents paramètres hémodynamiques invasifs et d'asynchronisme électrique (électrodes de contact épocardiques) ont été mesurés et comparés sur un modèle canin de BBG chronique (n=6) en rythme spontané, lors d'une stimulation mono-VG et d'une stimulation BIV. Les procédures ont été réalisées dans le laboratoire du professeur Prinzen à Maastricht.

Etude clinique : différents paramètres hémodynamiques invasifs et d'asynchronisme électrique (cartographie électrocardiographique non invasive) ont été mesurés et comparés chez des patients en insuffisance cardiaque avec BBG (n=24) en rythme spontané, lors d'une stimulation mono-VG et d'une stimulation BIV. Les procédures ont été réalisées dans le service du professeur Haissaguerre à Bordeaux.

Modélisation informatique : sur la base des données animales et humaines, la mécanique et l'hémodynamique cardiaque ont pu être simulées sur le modèle d'insuffisance cardiaque avec bloc de branche gauche (CircAdapt) avec comparaison du rythme spontané, d'une stimulation mono-VG et d'une stimulation BIV. Pour cette étude le modèle numérique CircAdapt a été amélioré autorisant une sous segmentation des murs VD, septal et VG (pour un total de 23 segments). Ce modèle permet l'évaluation du stress pariétal et du strain circonférentiel (réalisation de boucles strain-stress). Le travail cardiaque segmentaire correspond à l'aire de la courbe strain-stress multipliée par le volume du segment analysé (en J/battement).

Nous avons observé des résultats similaires entre études animales et études chez l'homme : 1) la stimulation mono-VG permettait un bénéfice hémodynamique significatif par rapport à l'activation spontanée sans réduction du temps d'activation ventriculaire gauche ou du temps d'activation ventriculaire total. La stimulation mono-VG se caractérisait par une inversion de la séquence d'activation ventriculaire par rapport à l'activation spontanée de BBG, chez l'animal comme chez l'homme. 2) la stimulation mono-VG permettait un bénéfice hémodynamique

similaire à la stimulation BIV en dépit de temps d'activation ventriculaire gauche ou total significativement prolongés par rapport à une stimulation BIV.

Nous avons retrouvé les mêmes résultats sur le modèle informatique (bénéfice hémodynamique équivalent en dépit de l'absence de réduction de l'asynchronisme ventriculaire). Les trois conditions (conduction spontanée avec BBG, stimulation mono-VG et BIV) se caractérisaient par des profils de strains segmentaires très différents. Les différences de charge observées étaient également très différentes, se traduisant par des différences du travail segmentaire estimé et par des différences de l'influence respective de chaque segment ou paroi sur la mécanique cardiaque globale. En présence d'un bloc de branche gauche, la paroi libre du ventricule gauche présente un travail augmenté et contribue majoritairement à l'efficacité (amoindrie) myocardique. La stimulation mono-VG redistribue la charge vers la paroi septale avec une baisse de la contribution de la paroi latérale VG résultant en un travail VG équivalent à celui observé lors d'un BBG. En revanche, durant la stimulation mono-VG, le travail VD est augmenté par rapport à celui observé lors d'un BBG, le travail global cardiaque (VD+VG) se trouvant donc majoré. La stimulation BIV permet une distribution plus homogène du travail VG et en une augmentation similaire du travail cardiaque global, mais cette fois grâce à une augmentation simultanée du travail des deux ventricules.

12.3 CONCLUSION

Ce travail a permis d'apporter de nouvelles données dans la compréhension des mécanismes impliqués dans la « resynchronisation » cardiaque. Les 3 modèles retrouvent 1) une efficacité supérieure de la stimulation mono-VG par rapport au rythme spontané (BBG) sans aucune réduction des niveaux d'asynchronisme ventriculaire. La séquence d'activation lors d'une stimulation mono-VG (paroi latérale vers septum, ventricule gauche précédant le ventricule droit) semble inversée par rapport à celle du BBG (paroi septale avant la paroi latérale et ventricule droit précédant le ventricule gauche). Il est donc possible d'améliorer la mécanique cardiaque par stimulation sans réduire l'asynchronisme mais en inversant les conditions de charge et en modifiant l'interaction ventriculaire. Le terme « resynchronisation » ne semble donc pas adéquat pour une thérapie basée sur une stimulation mono-VG. 2) une efficacité égale

de la stimulation ventriculaire gauche par rapport à la stimulation BIV avec pour cette dernière une réduction significative des différents niveaux d'asynchronisme ventriculaire et une meilleure homogénéité de la répartition du travail myocardique. Ces résultats posent la question du choix du mode de stimulation pour un patient donné. L'amélioration de la mécanique cardiaque lors d'une stimulation ventriculaire gauche s'appuie sur un travail accru du ventricule droit. En présence d'une dysfonction ventriculaire droite majeure, les possibilités de bénéfice après stimulation mono-VG semblent réduites. A l'opposé, si la fonction ventriculaire droite intrinsèque est préservée et la fonction ventriculaire gauche très altérée, ce mode de stimulation pourrait être privilégiée.

Nous allons dans un futur proche réaliser différentes expérimentations couplant ces modèles d'insuffisance cardiaque pour tester ces hypothèses.

Comparative Electromechanical and Hemodynamic Effects of Left Ventricular and Biventricular Pacing in Dyssynchronous Heart Failure

Electrical Resynchronization Versus Left–Right Ventricular Interaction

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Objectives

The purpose of this study was to enhance understanding of the working mechanism of cardiac resynchronization therapy by comparing animal experimental, clinical, and computational data on the hemodynamic and electromechanical consequences of left ventricular pacing (LVP) and biventricular pacing (BiVP).

Background

It is unclear why LVP and BiVP have comparative positive effects on hemodynamic function of patients with dyssynchronous heart failure.

Methods

Hemodynamic response to LVP and BiVP (% change in maximal rate of left ventricular pressure rise [$\text{LVdP}/\text{dt}_{\text{max}}$]) was measured in 6 dogs and 24 patients with heart failure and left bundle branch block followed by computer simulations of local myofiber mechanics during LVP and BiVP in the failing heart with left bundle branch block. Pacing-induced changes of electrical activation were measured in dogs using contact mapping and in patients using a noninvasive multielectrode electrocardiographic mapping technique.

Results

LVP and BiVP similarly increased $\text{LVdP}/\text{dt}_{\text{max}}$ in dogs and in patients, but only BiVP significantly decreased electrical dyssynchrony. In the simulations, LVP and BiVP increased total ventricular myofiber work to the same extent. While the LVP-induced increase was entirely due to enhanced right ventricular (RV) myofiber work, the BiVP-induced increase was due to enhanced myofiber work of both the left ventricle (LV) and RV. Overall, $\text{LVdP}/\text{dt}_{\text{max}}$ correlated better with total ventricular myofiber work than with LV or RV myofiber work alone.

Conclusions

Animal experimental, clinical, and computational data support the similarity of hemodynamic response to LVP and BiVP, despite differences in electrical dyssynchrony. The simulations provide the novel insight that, through ventricular interaction, the RV myocardium importantly contributes to the improvement in LV pump function induced by cardiac resynchronization therapy. (J Am Coll Cardiol 2013;62:2395–403) © 2013 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with chronic heart failure (HF), decreased left ventricular (LV) ejection fraction ($\leq 35\%$), and left bundle branch block (LBBB) (1,2). Its working

action is generally believed to originate from resynchronization of the LV and right ventricular (RV) electrical activation, achieved by biventricular pacing (BiVP).

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Fédération Française de Cardiologie." Dr. Gorcsan has received research grants from Biotronik, Medtronic, Toshiba, and St. Jude Medical; and is a consultant for CardioInsight Technologies Inc, GE, Toshiba, Biotronik, Medtronic, and St. Jude Medical. Drs. Strom and Ramanathan are paid employees and stock owners of CardioInsight Technologies Inc. Dr. Ritter has served as a consultant for Sorin CRM and Medtronic and has received consultant honoraria. Drs. Haïssaguerre and Jaïs are stock owners of CardioInsight Technologies Inc. Dr. Prinzen has received research grants from Medtronic, EBR Systems, and Merck Sharp & Dohme. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 1, 2013; revised manuscript received July 11, 2013, accepted August 6, 2013.

Abbreviations and Acronyms

ANOVA = analysis of variance

AT_{TOT} = total ventricular activation time

AV = atrioventricular

BiVP = biventricular pacing

CRT = cardiac resynchronization therapy

ECM = electrocardiographic mapping

HF = heart failure

LBBB = left bundle branch block

LV = left ventricle/ventricular

LVdP/dt_{max} = % change in maximal rate of left ventricular pressure rise

LVP = left ventricular pacing

RV = right ventricle/ventricular

RVdP/dt_{max} = % change in maximal rate of right ventricular pressure rise

Paradoxically, single-site left ventricular pacing (LVP) has been shown to be as beneficial as BiVP for LV systolic pump function in acute hemodynamic studies (3–5), in long-term follow-up studies (6–8), and even in situations

See page 2404

where LVP is unlikely to result in fusion of 2 activation wave fronts induced by LVP and intrinsic conduction (5,9). Therefore, the question arises whether electrical resynchronization is the primary working mechanism underlying the functional improvement induced by CRT. It is well known that ventricular pacing redistributes mechanical work in the LV wall so that the region of latest activation is associated with highest mechanical work (10). However, it is not known to what extent ventricular pacing affects mechanical work generated by the

RV myocardium. Because direct mechanical coupling of the ventricles allows transmission of myocardial work between the ventricles, we hypothesize that a pacing-induced increase of RV myocardial work can benefit LV pump function.

To test this hypothesis, we measured local electrical and global hemodynamic function in an animal model of chronic HF with LBBB and in CRT candidates during baseline (LBBB), LVP, and BiVP. Furthermore, we used a computer model of the human heart and circulation (11–13) to investigate the consequences of LVP and BiVP for local LV and RV tissue mechanics. Together, these complementary data provide novel insights in the working mechanism of CRT, especially regarding the involvement of the RV myocardium in its hemodynamic effect.

Methods

Animal experiments. Animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (86/609/EU). The protocol was approved by the Experimental Animal Committee of Maastricht University.

In 6 adult mongrel dogs (29 ± 3 kg), LBBB was induced by radiofrequency ablation and, subsequently, HF was induced by 4 weeks of tachypacing (14). Continuous, invasive hemodynamic and electrocardiographic measurements were performed during right atrial pacing at approximately 10 beats/min above intrinsic heart rate (baseline) and during

atrial paced LVP and BiVP at the same heart rate and at short atrioventricular (AV) delay, ensuring full ventricular capture as noticed on the surface electrocardiogram. More details of the experimental protocol are provided in [Online Appendix A](#).

Electrical activation maps were used to calculate 2 indexes of electrical dyssynchrony: total ventricular activation time (AT_{TOT}) derived from all electrodes and LV activation time derived from the septal and LV free wall electrodes only (14).

Patient measurements. The execution of the study conformed to the principles outlined in the Declaration of Helsinki on research in human subjects. The study protocol was approved by the Medical Ethics Committee of CHU Bordeaux. All patients granted their written approval to participate in the study.

PATIENT POPULATION. The study included 24 consecutive patients who fulfilled the following criteria: 1) New York Heart Association functional class II, III, or IV, despite optimal medical therapy; 2) LV ejection fraction ≤35% during sinus rhythm; 3) QRS duration ≥120 ms; and 4) LBBB morphology on the surface electrocardiogram. Both QRS duration and LBBB morphology were defined according to the most recent American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendations (15). Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in 1 or more of the major epicardial coronary arteries), history of myocardial infarction, or prior revascularization.

DEVICE IMPLANTATION, PACING PROTOCOL, AND ASSESSMENT OF HEMODYNAMIC FUNCTION. All patients were implanted with a CRT device with leads in the RV apex and in a lateral or posterolateral branch of the coronary sinus. Within 72 h after device implantation, a high-fidelity pressure-recording micromanometer (Radi Medical Systems, St. Jude Medical, St. Paul, Minnesota) was introduced in the LV cavity. LV pressure data were acquired (16) during baseline (AAI mode; 10 beats/min above intrinsic heart rate) and during atrial paced LV and biventricular stimulation (DDD mode). The AV delay was set to the longest delay that did not lead to fusion between electrical activation waves originating from intrinsic RV conduction and from the LV pacing electrode during LVP. The same AV delay was used during BiVP with simultaneous LV-RV stimulation. Hemodynamic response was defined as % change in maximal rate of LV pressure rise (LVdP/dt_{max}) relative to baseline.

NONINVASIVE ELECTROCARDIOGRAPHIC MAPPING. In a subset of 10 patients, we used noninvasive, high-resolution electrocardiographic mapping (ECM) (CardioInsight Technologies Inc., Cleveland, Ohio) to acquire ventricular epicardial activation maps during baseline, LVP, and BiVP (17,18) and to

Table 1 Electrical and Hemodynamic Data From Dogs With Chronic HF and LBBB (N = 6) During Baseline, LVP, and BiVP

	Baseline	LVP	BiVP	ANOVA	p Values		
					Baseline vs. LVP	Baseline vs. BiVP	LVP vs. BiVP
QRS duration (ms)	122 ± 10	132 ± 26	115 ± 15	0.098	—	—	—
Heart rate (beats/min)	134 ± 11	133 ± 10	133 ± 10	0.368	—	—	—
AT _{TOT} (ms)	95 ± 16	106 ± 22	84 ± 13	0.008	0.160	0.002	0.022
AT _{LV} (ms)	95 ± 16	96 ± 14	83 ± 13	<0.001	0.701	0.001	0.003
LV stroke volume (ml)	15 ± 5	17 ± 11	18 ± 7	0.428	—	—	—
LV pump stroke work (ml × mm Hg)	1,022 ± 503	1,245 ± 883	1,230 ± 499	0.256	—	—	—
LV peak systolic pressure (mm Hg)	77 ± 11	79 ± 10	79 ± 10	0.105	—	—	—
LVdP/dt _{max} (mm Hg/s)	853 ± 99	1,023 ± 158	1,005 ± 127	0.034	0.038	0.035	0.295
LV end-diastolic pressure (mm Hg)	20 ± 13	19 ± 14	21 ± 15	0.279	—	—	—
LV end-diastolic volume (ml)	128 ± 37	124 ± 36	127 ± 35	0.223	—	—	—
RV peak systolic pressure (mm Hg)	32 ± 12	29 ± 11	31 ± 11	0.015	0.026	0.155	0.053
RVdP/dt _{max} (mm Hg/s)	442 ± 140	411 ± 146	463 ± 118	0.050	0.136	0.290	0.043
RV end-diastolic pressure (mm Hg)	8 ± 6	8 ± 4	9 ± 7	0.894	—	—	—

Values are mean ± SD.

AT_{LV} = left ventricular electrical activation time (including septum and left ventricular free wall); AT_{TOT} = total ventricular electrical activation time (including septum, left ventricular free wall, and right ventricular free wall); BiVP = biventricular pacing; dP/dt_{max} = maximal rate of pressure rise; HF = heart failure; LBBB = left bundle branch block; LV = left ventricular; LVP = left ventricular pacing; RV = right ventricular.

quantify electrical dyssynchrony (AT_{TOT} and LV activation time).

Simulations. The CircAdapt model of heart and circulation (11,19) was used to quantify the acute effects of LVP and BiVP on ventricular mechanics and hemodynamics of the failing heart with LBBB. The model consists of modules representing cardiac walls, cardiac valves, large blood vessels, systemic and pulmonary peripheral vasculature, the pericardium, and local cardiac myofiber mechanics (Online Appendix B). It enables realistic beat-to-beat simulation of cardiovascular mechanics and hemodynamics under a wide variety of (patho-)physiological circumstances, including ventricular mechanical dyssynchrony (12,13).

First, mechanics and hemodynamics of the normal cardiovascular system with nonfailing myocardium and synchronous activation of the ventricular walls were simulated, as published previously (12,13). Second, a failing heart with LBBB was simulated (Online Appendix C). Third, LVP and BiVP were simulated so that they were in agreement with the electrocardiographic mapping data obtained in the patients and dogs, that is, LVP did not change AT_{TOT} (135 ms), whereas BiVP was assumed to reduce AT_{TOT} from 135 to 60 ms (Online Appendix C).

LOCAL VENTRICULAR MYOFIBER MECHANICS. Simulated time courses of local Cauchy myofiber stress and natural strain were used to quantify regional differences in mechanical load and deformation of the myocardial tissue during LBBB, LVP, and BiVP. Peak systolic myofiber stress and external myofiber work were quantified as indexes of local myocardial tissue load. External myofiber work, expressed in joule per cardiac cycle (J/beat), was defined as the area enclosed by the stress-strain relation multiplied by tissue volume of the myocardial segment, which equaled 8.5 ml for each ventricular wall segment.

Statistical analysis. Values are presented as mean ± SD for continuous variables and as numbers and percentages for discrete variables. Statistical analysis was performed with the IBM SPSS Statistics 20 package for Windows (IBM Corp., Armonk, New York). Assumptions on homogeneity of variances and normality of residual distributions were checked using Mauchly's test of sphericity and Q-Q plots, respectively. One-way repeated measures analysis of variance (ANOVA) was used to test for significant effects of LVP and BiVP on baseline electrical and hemodynamic function parameters. If the sphericity assumption appeared to be violated, the Greenhouse-Geisser correction was used to adjust degrees of freedom for the averaged results of the ANOVA. If ANOVA showed significance, pairwise post-hoc analysis for differences between the 3 pacing conditions (no pacing/LVP/BiVP) was performed using the Fisher Least Significant Difference method. A p value <0.05 was considered statistically significant for all analyses.

Table 2 Baseline Patient Characteristics

	All Patients (n = 24)	ECM Subgroup (n = 10)
Age (yrs)	66 ± 12	66 ± 12
Male sex	17 (71%)	8 (80%)
NYHA functional class		
II	7 (29%)	4 (40%)
III	17 (71%)	6 (60%)
Ischemic etiology	8 (33%)	3 (30%)
QRS duration (ms)	164 ± 22	162 ± 24
PR interval (ms)	213 ± 30	225 ± 37
LV ejection fraction (%)	27 ± 3	26 ± 5

Values are mean ± SD or n (%).

ECM = electrocardiographic mapping; LV = left ventricular; NYHA = New York Heart Association.

Table 3	Electrical and Hemodynamic Patient Data During Baseline, LVP, and BiVP						
	Baseline	LVP	BiVP	ANOVA	p Values		
					Baseline vs. LVP	Baseline vs. BiVP	LVP vs. BiVP
All patients (N = 24)							
LVdP/dt _{max} (mmHg/s)	728 ± 221	844 ± 281	838 ± 250	<0.001	<0.001	<0.001	0.687
ECM subgroup (n=10)							
LVdP/dt _{max} (mm Hg/s)	737 ± 204	827 ± 251	822 ± 238	<0.001	0.006	0.001	0.666
AT _{TOT} (ms)	130 ± 12	131 ± 26	96 ± 14	0.004	0.915	0.001	0.014
AT _{LV} (ms)	112 ± 26	105 ± 15	89 ± 18	0.099	—	—	—

Values are mean ± SD.
Abbreviations as in Tables 1 and 2.

Results

Dogs and patients. Baseline conditions of dogs and patients are presented in Tables 1 and 2, respectively. Paced

AV delay was relatively short compared with the PR interval in dogs (86 ± 26 ms vs. 141 ± 40 ms, respectively) as well as in patients (106 ± 19 ms vs. 213 ± 30 ms).

LVP AND BiVP SIMILARLY IMPROVE SYSTOLIC LV FUNCTION. Both LVP and BiVP similarly increased LVdP/dt_{max} compared with baseline in dogs (LVP vs. BiVP; 21 ± 19% vs. 19 ± 17%; p = 0.33) (Table 1) and patients (16 ± 13% vs. 16 ± 11%; p = 0.95) (Table 3). Animal experimental data showed a trend toward increased LV stroke volume, pump stroke work, and systolic peak pressure during LVP and BiVP as compared with baseline, while LV end-diastolic volume and pressure remained unchanged (Table 1). In contrast, RV systolic peak pressure and maximal rate of right ventricular pressure rise (RVdP/dt_{max}) were decreased during LVP as compared with baseline and BiVP.

BiVP, BUT NOT LVP, REDUCES ELECTRICAL DYSSYNCHRONY. Ventricular electrical activation maps of dogs and patients revealed the same characteristics (Fig. 1): during baseline, a classical LBBB pattern of electrical activation starting at the lateral RV free wall and gradually spreading towards the lateral LV free wall; during LVP, a mirrored LV-to-RV pattern of epicardial activation; and during BiVP, 2 fusing wave fronts of activation originating from the LV and RV pacing sites. In addition, the canine data showed that the septum is activated in an RV-to-LV transmural direction during baseline and BiVP and in an LV-to-RV direction during LVP. Compared with baseline, BiVP significantly reduced electrical dyssynchrony in dogs and in patients (Fig. 2), whereas LVP did not. In the dogs, activation times were significantly shorter during BiVP than during LVP (Table 1). In the patients, only AT_{TOT} was significantly shorter during BiVP than during LVP (Table 3).

Simulations. The model simulations also showed that LVP and BiVP similarly increased LVdP/dt_{max} by 15% (Table 4), despite the longer ventricular activation time during LVP. As in the dogs, both pacing strategies increased LV stroke volume, pump stroke work, and systolic peak pressure (Table 4), and LVP decreased RVdP/dt_{max} compared with baseline. In addition, simulations revealed that both LVP and BiVP increased RV pump stroke work by 16%.

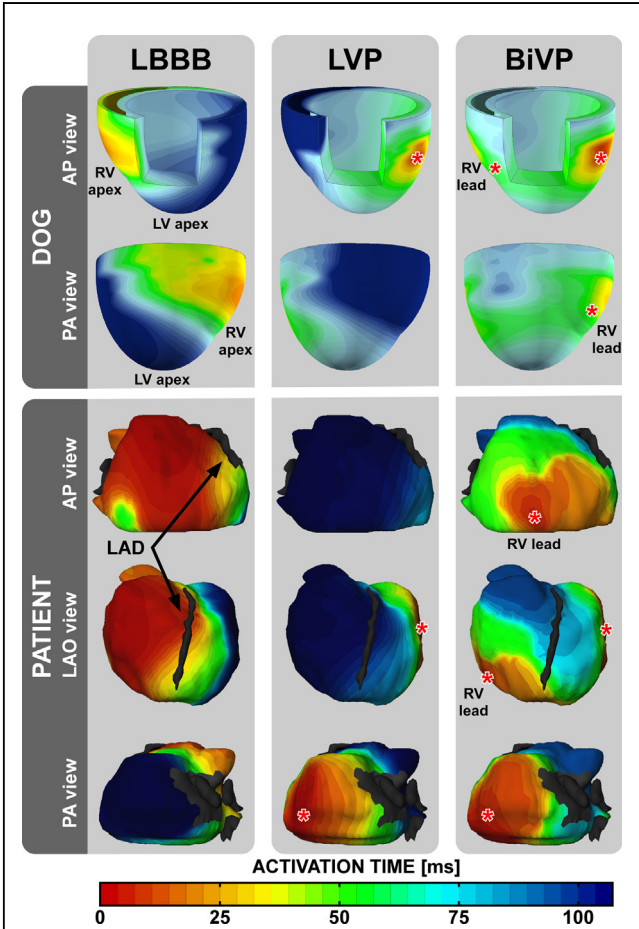
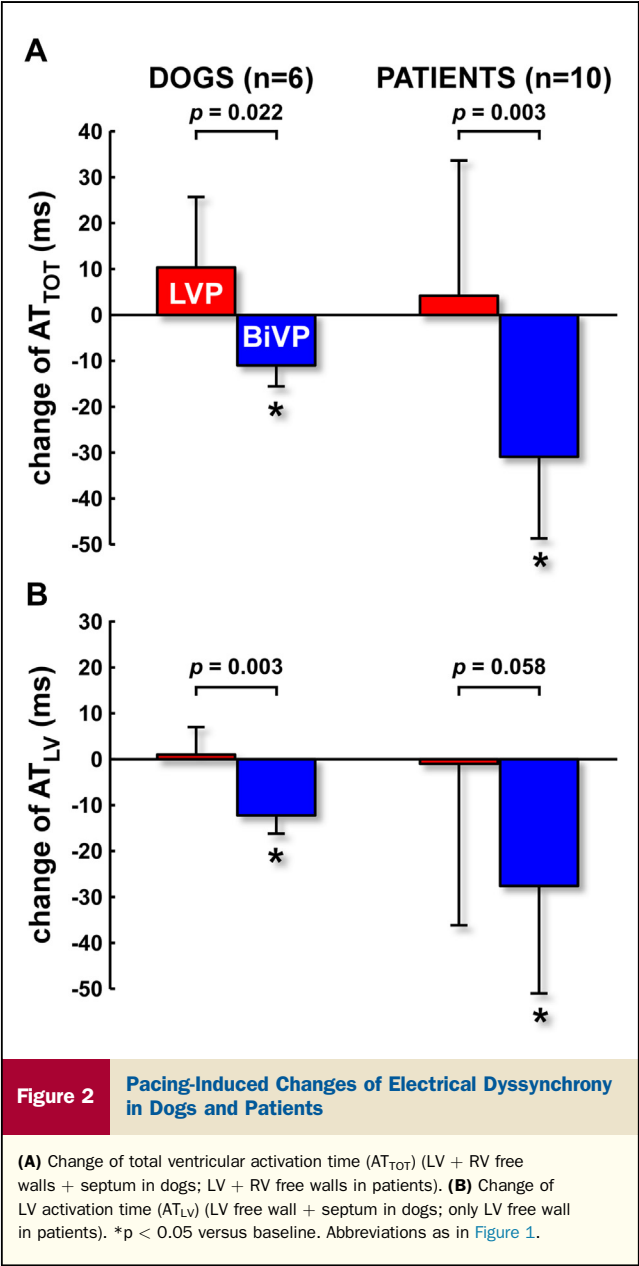


Figure 1 Electrocardiographic Mapping in a Dog and a Patient With Nonischemic Heart Failure and LBBB

Isochronal maps show the timing of electrical activation during baseline, left ventricular pacing (LVP), and biventricular pacing (BiVP). **Black arrows** indicate the left anterior descending coronary artery (LAD). The **gray section** in the posterior-anterior (PA) view represents the segmentation of the mitral orifice. **Red asterisks** indicate pacing sites. AP = anterior-posterior; LAO = left anterior oblique; LBBB = left bundle branch block; LV = left ventricular; RV = right ventricular.



LVP AND BiVP DIFFERENTLY AFFECT LOCAL VENTRICULAR MYOFIBER MECHANICS. Pronounced local differences are present in the pattern and amplitude of myofiber strain during baseline (LBBB), LVP, and BiVP (Fig. 3). Early-activated segments are characterized by rapid onset of systolic myofiber shortening followed by rebound stretch and, in some cases, a second phase of shortening at the end of systole. In late-activated regions, early-systolic stretch is followed by pronounced systolic myofiber shortening.

The regional differences in strain patterns translated into differences in local mechanical tissue load (Fig. 3: color maps). In the LBBB simulation, most mechanical myofiber work was generated by the LV free wall segments, whereas the RV free wall and septal segments generated little mechanical work or even dissipated mechanical work, as

Table 4	Electrical and Hemodynamic Data Derived From Computer Simulations of a Failing Heart During LBBB, LVP, and BiVP		
	LBBB	LVP	BiVP
Heart rate (beats/min)	80	80	80
AV delay (ms)	220	100	100
AT _{TOT} (ms)	135	135	60
AT _{LV} (ms)	120	120	60
LV stroke volume (ml)	53	61	62
LV pump stroke work (ml × mm Hg)	4,911	6,289	6363
LV peak systolic pressure (mm Hg)	113	128	127
LVdP/dt _{max} (mm Hg/s)	710	815	818
LV end-diastolic pressure (mm Hg)	19	24	25
LV ejection fraction (%)	23	25	25
RV pump stroke work (ml × mm Hg)	1,641	1,913	1,906
RV peak systolic pressure (mm Hg)	36	36	36
RVdP/dt _{max} (mm Hg/s)	328	270	290
RV end-diastolic pressure (mm Hg)	5	5	6

Abbreviations as in Table 1.

evidenced by the clockwise stress-strain relations (Fig. 3). Compared with LBBB, LVP reallocated mechanical work from the LV free wall to the septum, resulting in a spatially mirrored but equally dispersed distribution of mechanical work over the LV myocardium. BiVP was associated with less early-systolic myofiber stretch and shortening and a more homogeneous distribution of myofiber work than LVP (Fig. 3). In contrast, LV peak systolic myofiber stress was more homogeneously distributed during LVP, whereas the average values did not differ between LVP and BiVP (92 ± 7 kPa and 92 ± 13 kPa, respectively).

LBBB and LVP were associated with a comparable net amount of mechanical myofiber work generated by the LV myocardium (Fig. 4). The RV myocardium, however, generated more work during LVP than during LBBB. As a result, LVP acutely increased total ventricular myofiber work by 25%. BiVP resulted in a similar increase of total myofiber work (23%) as LVP, but now due to an increase of both LV and RV myofiber work.

VENTRICULAR INTERACTION: CONTRIBUTION OF RV MYOCARDIUM TO LV PUMP FUNCTION. A more precise study on the role of left-right ventricular interaction on hemodynamic response to pacing therapy was performed by simulating LVP and BiVP with 5 different AV delays (60/80/100/120/140 ms) as well as 5 different velocities of activation, which resulted in a range of values for AT_{TOT} (24/36/48/60/72 ms during BiVP and 54/81/108/135/162 ms during LVP). For the resulting 50 simulations, Figure 5 shows the relationship between ventricular myofiber work and $LVdP/dt_{max}$. The left panel indicates that total ventricular myofiber work increased linearly with $LVdP/dt_{max}$ and that this linear relationship was virtually independent of the pacing mode. However, LVP and BiVP behaved differently when considering LV and RV myofiber work separately (Fig. 5, middle and right panel, respectively). While LVP and BiVP

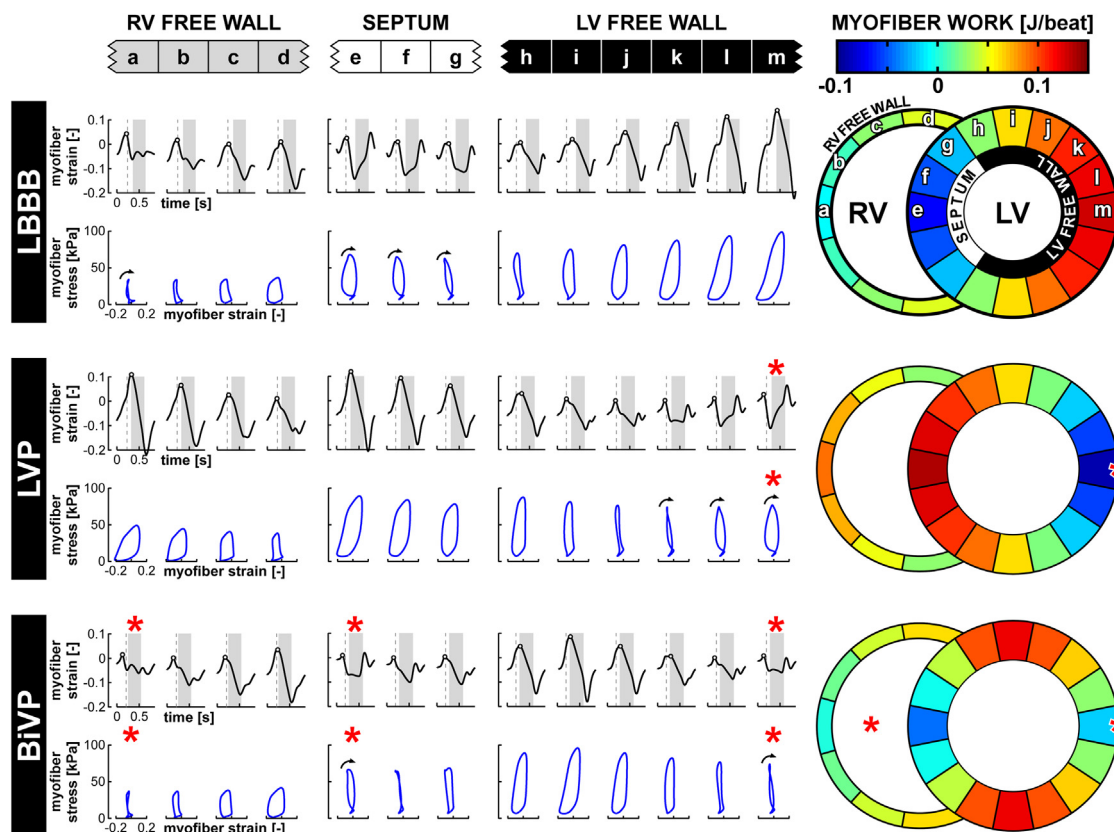


Figure 3 Simulated Local Myofiber Mechanics in a Failing Heart During LBBB and Pacing

Time courses of natural myofiber strain are plotted in **black**. **Red asterisks** indicate pacing sites. **Vertical dashed lines** indicate moment of mitral valve closure, and LV ejection is highlighted in **gray**. **Black circles** indicate onset of systolic shortening. Relations between myofiber stress and myofiber strain are plotted in **blue**. **Black arrows** indicate segments with a clockwise stress-strain relation, indicating negative myofiber work. **Color maps** indicate myofiber work per ventricular wall segment. Abbreviations as in Figure 1.

can lead to the same total ventricular myofiber work and $LVdP/dt_{max}$, their distribution of myofiber work over the LV and RV myocardium is rather different. During BiVP, the relative contribution of the RV myocardium to total ventricular myofiber work was rather constant and ranged from 22% to 24%. This contribution was considerably more variable during LVP, and increased from 28% in the simulation with highest conduction velocity to 38% in that with lowest. Overall, these simulation data highlight the important role of the RV myocardium as a contributor to LV pump function during LVP and, thus, the importance of ventricular interaction during CRT.

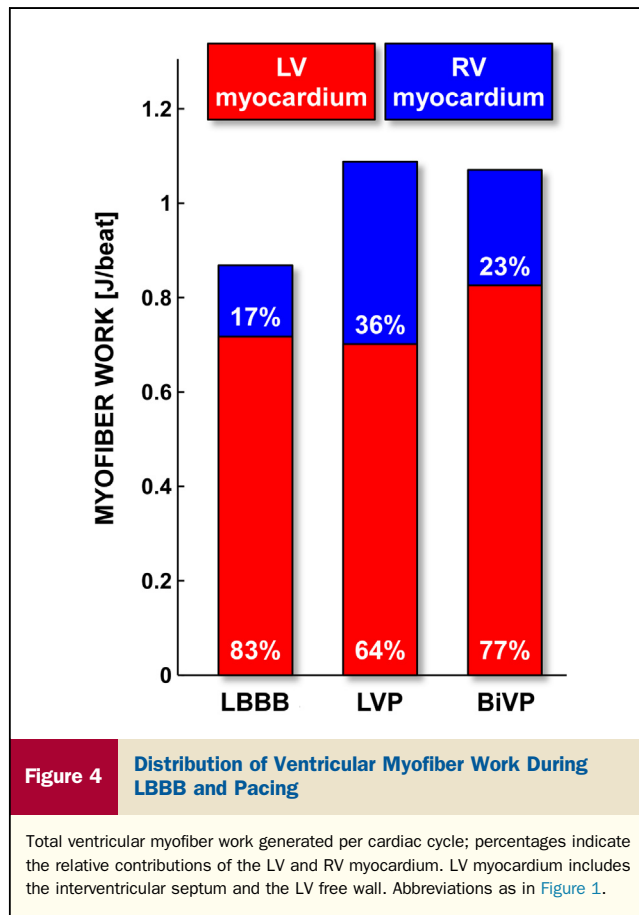
Discussion

In the present study, we demonstrate that LVP and BiVP improve the systolic function of the dyssynchronous failing heart to a similar extent, both in experimental animals and in patients. With state-of-the-art techniques for electrical mapping, we showed in patients that pacing-induced hemodynamic improvement can occur without electrical resynchronization. These findings are corroborated by computer

simulations, which showed that both pacing strategies increase total ventricular myofiber work to a similar extent, yet differently redistribute myofiber load over the LV and RV myocardium. Overall, LV systolic function correlates better with total ventricular myofiber work rather than with LV or RV myofiber work alone. These data provide the novel insight that left–right ventricular interaction is an important determinant of the hemodynamic effect of pacing therapy in dyssynchronous HF.

RV mechanical work: the missing link in the explanation for similarity of response to LVP and BiVP? Our finding that LVP and BiVP improve LV systolic function to the same extent corroborates previously published data on acute hemodynamic response (3,4) and on long-term clinical response and reverse remodeling (6–8). In addition, the present study provides a potential mechanism underlying these observations.

It is known that contractile harmony is substantially disturbed in patients with LBBB or pacing-induced electrical dyssynchrony and that this contractile discordance compromises cardiac pump function. Regional differences in the systolic deformation pattern are related to local differences in



sarcomere length and, consequently, myofiber contractile force (20) and work load (10). The simulations are in close agreement with experimental findings demonstrating that mechanical myofiber work is small or even negative in regions close to the pacing site and large in regions remote from the pacing site (10). So far, these insights remained limited to the LV wall. Our simulations show that the RV myocardium contributes significantly to the improvement of LV pump function in pacing therapies, especially LVP. While it may be intuitive that BiVP improves LV pump function by increasing LV myofiber work, it may be less intuitive that LVP similarly improves LV systolic pump function by exclusively increasing the amount of mechanical work generated by the RV myocardium. These findings emphasize the importance of ventricular interaction, that is, the property that the RV myocardium contributes to LV systolic pump function and vice versa.

Simulations of LVP and BiVP in hearts with different conduction velocities (Fig. 5) revealed that, during LVP, the relative contribution of RV myofiber work to total ventricular myofiber work increased with total ventricular activation time, whereas it stayed constant during BiVP. These simulation data suggest that LVP is less effective than BiVP in patients with slow intramyocardial conduction, with diminished RV contractile function, or in whom mechanical ventricular interaction is being impeded.

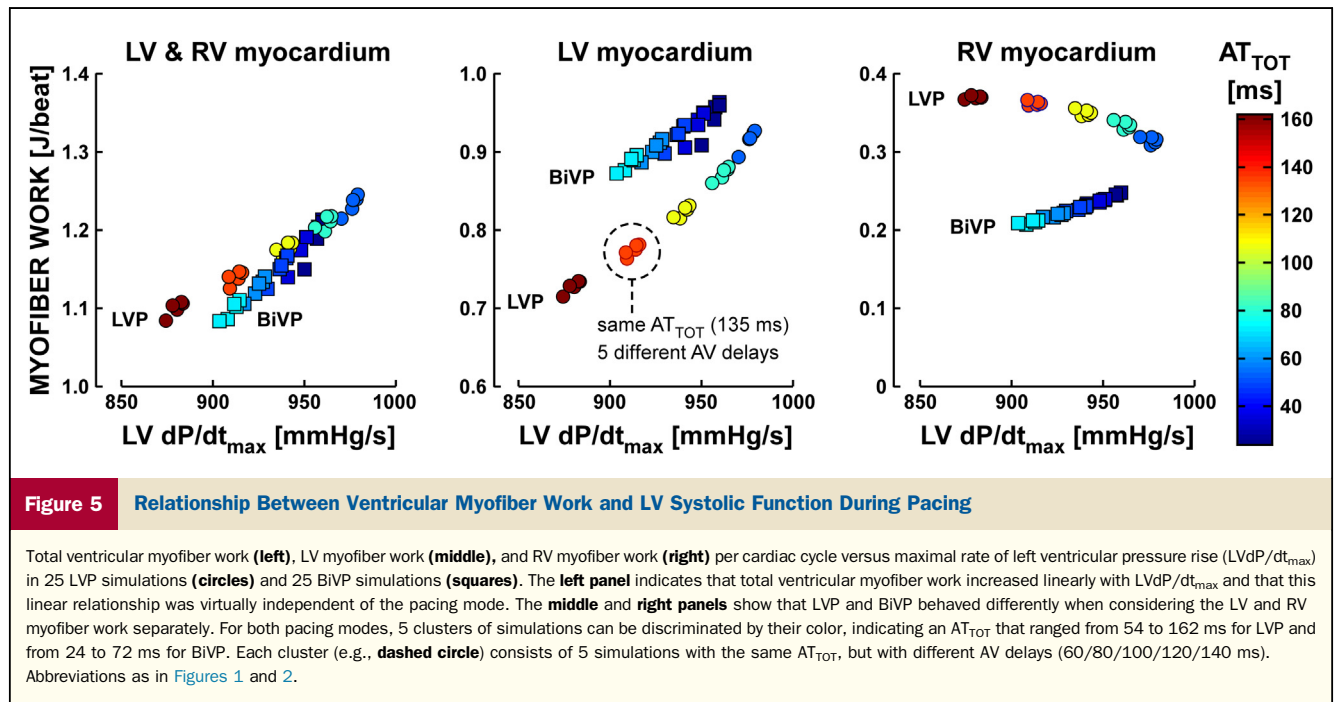
While indirect hemodynamic interaction results from the series coupling of the ventricles via the pulmonary and systemic circulations, direct mechanical interaction is due to the anatomical coupling via the interventricular septum and the surrounding pericardium (21). Because our animal experiments show no direct effect of LVP on indexes of LV filling, such as LV end-diastolic pressure and volume (Table 1), the positive effect of LVP on LV systolic pump function most probably results from direct mechanical interaction. Furthermore, the decreased values of RV systolic pressure and $RVdP/dt_{max}$ with LVP suggest that the extra amount of mechanical work generated by the RV myocardium is largely converted into LV pump work through direct mechanical interaction.

Clinical implications and future perspectives. The demonstration that, during CRT, the RV myocardium can contribute to LV pump function and that this contribution differs between LVP and BiVP may explain why some patients respond better to LVP and others to BiVP, as demonstrated in the GREATER-EARTH (Evaluation of Resynchronization Therapy for Heart Failure in patients with a QRS duration >120 ms) study (6). We hypothesize that local differences in myocardial contractility (e.g., due to infarction, hibernation, and so on) determine a patient's response to LVP and BiVP in a way that hemodynamic improvement is compromised when the region with impaired contractile function coincides with the location of latest activation and, hence, highest mechanical load. Although experimental data point in this direction (22), it remains to be confirmed with prospective clinical studies.

Many studies demonstrated the acute deleterious effect of RV pacing on LV systolic function in terms of $LVdP/dt_{max}$ (3,4). Similarly, our experimental and simulation data revealed that LVP acutely decreased $RVdP/dt_{max}$ (Tables 1 and 4). Our simulations, however, additionally showed that RV pump stroke work was increased during both LVP and BiVP (Table 4). Therefore, it is questionable whether the pacing-induced decrease of $RVdP/dt_{max}$ should be considered a sign of acute RV systolic impairment. Our simulations also showed that LVP increased mechanical myofiber work of the RV myocardial tissue by more than 100% (Fig. 4). Whether this acute LVP-induced increase of RV tissue load translates into compensatory RV remodeling and eventually RV decompensation and failure remains unknown and should be subject of future research.

Study limitations. In the present study, we evaluated the acute hemodynamic effect of CRT. Whether the observed acute hemodynamic improvements will evolve in chronic response to CRT, in terms of hard clinical endpoints or reverse remodeling, is unclear and should be the subject of future research.

In dogs and patients, LVP and BiVP were applied with atrial pacing at a short AV delay to ensure a constant heart rate and the absence of fusion between electrical activation waves originating from intrinsic conduction and from pacing electrode(s). These conditions have been chosen to clearly



show the proof of principle that a pacing-induced hemodynamic benefit can be obtained in the absence of fusion in the case of LVP. Hence, our study is conceptually different from a previous study showing noninferiority of fusion-synchronized LVP compared with conventional simultaneous BiVP (23). We acknowledge that the AV delays used in our study may not have been the ones leading to optimal LV filling or systolic function. In a previous acute hemodynamic study (3), however, maximal aortic systolic or pulse pressure was observed at an AV delay of approximately $0.5 \times (\text{PR interval} - 30 \text{ ms})$ for both LVP and BiVP. Applying this formula to our patient data, we obtained a predicted optimal AV delay of $92 \pm 15 \text{ ms}$, which is close to the AV delay programmed in this study ($106 \pm 19 \text{ ms}$). Furthermore, the average paced AV delay in the patients was in good agreement with the value reported by Thibault et al. (6) in the GREATER-EARTH study ($101 \pm 16 \text{ ms}$), a study that also compared the effectiveness of LVP and BiVP in a conventional CRT population.

The multimodality of our study approach may have complicated interpretation of the results. At the same time, however, the consistency of the hemodynamic and electrocardiographic response to LVP and BiVP in animals, patients, and simulations provides firm evidence that electrical resynchronization is not always required for pacing therapy to improve systolic cardiac pump function. The invasive ECM data obtained in the dogs served as a control technique for our clinical ECM data, which was obtained by noninvasive indirect mapping of epicardial electrical activation. The animal experimental protocol also included measurement of RV pressure data. These data enabled evaluation of the effects of LVP and BiVP on RV systolic function. The simulation data for RV function showed good

agreement with the experimental data, that is, LVP was associated with lower RVdP/dt_{max} than BiVP.

The computational model used in this study inherently provides a simplified representation of an average patient's failing heart with LBBB. Therefore, the conclusions drawn from these data should be interpreted with care. However, many model predictions agreed with measurements in patients and experimental animals. Moreover, the simplifications allowed a transparent view on complex fundamental mechanisms, which are hard to assess in experimental or clinical settings.

Conclusions

LVP and BiVP improve LV hemodynamic function to the same extent, despite substantial differences in electrical dyssynchrony. Both pacing strategies similarly increase total ventricular myofiber work, which is tightly linked with LV pump function. Our simulations show that CRT can improve LV systolic function by mechanical recruitment of the RV myocardium.

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Key Words: ventricular interaction ■ myocardial work ■ cardiac resynchronization therapy ■ dyssynchrony ■ electrophysiology mapping.

APPENDIX

For supplemental information detailing the animal experiment protocol, model description, and simulation protocol, please see the online version of this article.

13 STIMULATION ENDOCARDIQUE VG ET STIMULATION MULTIPOINTS COMME NOUVELLES STRATEGIES POUR L'APPLICATION DE LA THERAPIE DE RESYNCHRONISATION CARDIAQUE.*, **

*Ploux S, Barandon L, Ritter P, Bordachar P: Positive hemodynamic and clinical response to tri-left ventricular pacing in a nonresponder to traditional cardiac resynchronization therapy. Heart Rhythm Off J Heart Rhythm Soc.⁷⁶

** Ploux S, Whinnett Z, Bordachar P: Left ventricular endocardial pacing and multisite pacing to improve CRT response. J Cardiovasc Transl Res 2012.⁷⁷

Dans cette revue, nous avons repris la littérature concernant 2 stratégies susceptibles de permettre une amélioration de la réponse après resynchronisation : la stimulation endocardique ventriculaire gauche et la stimulation multipoints.

13.1 LA STIMULATION ENDOCARDIQUE VENTRICULAIRE GAUCHE

13.1.1 Rationnel

Sur le plan théorique, une stimulation endocardique ventriculaire gauche présente un certain nombre d'avantages : 1) L'abord transseptal permet d'avoir un choix réel du site de stimulation à l'opposé de l'implantation par le sinus coronaire où le site est le plus souvent imposé par les contraintes anatomiques. En plus d'un avantage hémodynamique évident, ce choix permet une optimisation des seuils de stimulation qui est un facteur parfois limitant lors d'une implantation par le sinus coronaire. De même, le risque de stimulation phrénique, autre facteur très limitant, peut être considéré comme inexistant. 2) La stimulation endocardique ventriculaire gauche apparaît plus physiologique que la stimulation épicaudique avec un respect du gradient d'activation endocarde-épicaudique et pourrait avoir moins d'effet pro-arythmique. 3) La resynchronisation BIV traditionnelle est associée avec un taux de non répondeurs incompressible dépassant les 30%. Dans 2 études récentes, la stimulation endocardique ventriculaire gauche a permis un bénéfice hémodynamique supérieur à la stimulation épicaudique, ce qui suggère un effet potentiel sur la qualité de la réponse clinique.

13.1.2 Aspects techniques

Le positionnement d'une sonde endocardique ventriculaire gauche par voie transseptale nécessite la ponction du septum inter-auriculaire pour permettre le passage de la sonde de l'oreillette droite à l'oreillette gauche puis le passage de l'oreillette gauche au ventricule gauche à travers la valve mitrale. Plusieurs équipes ont réalisé et décrit l'implantation définitive d'une sonde de stimulation ventriculaire gauche par voie transseptale soit par voie haute soit à l'aide d'une approche mixte couplant voie haute et voie basse.⁷⁸⁻⁸¹ Quelle que soit la technique, les résultats semblent satisfaisants en termes de succès opératoires et de complications. Les résultats publiés portant sur la stabilité de la sonde et des seuils de stimulation sont également rassurants mais concernent un nombre limité de patients.

Tout élargissement possible des indications de cette voie d'abord doit être précédé par le développement de matériel dédié de façon à faciliter l'implantation. L'étude Alsync, étude multicentrique dont l'objectif est de valider la faisabilité et la sécurité d'un nouveau dispositif développé par la société Medtronic permettant l'implantation par voie sous-clavière d'une sonde ventriculaire gauche endocardique, vient de se terminer. Les résultats semblent plutôt positifs avec une faisabilité élevée et un risque de complications limité.

13.1.3 Niveau de preuve

Etudes animales : sur un modèle canin de BBG et sur un modèle canin d'infarctus et de BBG il a été démontré que 1) la stimulation endocardique permet une réduction significative de l'asynchronisme électrique par rapport au rythme spontané de l'animal mais également par rapport à la stimulation épicaudique 2) la stimulation endocardique permet un bénéfice hémodynamique significatif et substantiel par rapport à la stimulation épicaudique au même site 3) le site de stimulation est déterminant lors d'une stimulation épicaudique. En revanche, il existe moins de disparités lors d'une stimulation de l'endocarde.⁸²⁻⁸⁴

Etudes chez l'homme : une étude réalisée dans notre centre a permis de montrer: 1) il n'existe pas un même site optimal ou délétère pour tous les patients. Effectivement, nous avons retrouvé de grandes disparités entre les patients en termes de site optimal ou de site procurant les plus mauvais résultats 2) le choix du site de stimulation a un impact variable suivant les

patients. En effet, chez certains patients, quel que soit le site testé, les variations hémodynamiques sont modestes. A l'opposé, chez certains patients, nous avons observé des résultats diamétralement opposés en fonction du site 3) l'optimisation du site de stimulation permet un bénéfice significatif pour tous les paramètres testés 4) la comparaison entre stimulation épicaudique et endocardique au même site donne un bénéfice significatif en faveur de la stimulation endocardique sur la fonction diastolique uniquement ($dp/dt_{\min}VG$).⁸⁵

L'expérience humaine sur l'efficacité de la stimulation endocardique au long cours est aujourd'hui encore assez limitée.⁸⁶

13.1.4 Complications potentielles

Le risque de constitution d'un thrombus autour de la sonde est un facteur limitant important du positionnement de la sonde à l'intérieur de la cavité ventriculaire gauche. En effet, les complications emboliques peuvent revêtir un caractère bien plus marqué pour une sonde située dans le VG en raison du risque d'embolie systémique et d'accident vasculaire cérébral. Très peu de patients ont bénéficié de l'implantation délibérée d'une sonde endocardique ventriculaire gauche. Ils bénéficiaient tous d'un traitement par anticoagulant au long cours. Le suivi et le nombre limité de patients ne permettent pas de tirer de conclusions définitives. Le risque d'accident vasculaire cérébral suivant l'implantation d'une sonde endocardique ventriculaire gauche a récemment été estimé à 6%/an sur une cohorte de 51 patients (anti-coagulés pour un INR cible compris entre 3.5 et 4.5).⁸⁷

L'abord transseptal pour positionner une sonde dans le ventricule gauche implique la traversée par la sonde de la valve mitrale. Les données de la littérature montrent que le peu de patients implantés par voie transseptale présentait soit une absence de modification de la fuite mitrale soit même une réduction significative de cette fuite mitrale, la réduction de l'asynchronisme ventriculaire et le remodelage inverse expliquant probablement ce phénomène.

L'existence d'une infection de matériel pourrait être difficile à gérer chez ce type de patient. En effet, une extraction percutanée paraît trop risquée devant le risque d'embolisation systémique d'une végétation, d'un thrombus ou même de fibrose enveloppant la sonde. Une intervention chirurgicale pourrait être proposée de façon systématique.

13.1.5 Perspectives

Le développement de cette voie d'abord nécessite donc la réalisation d'études permettant de valider la faisabilité et la sécurité mais également l'intérêt clinique potentiel pour le patient. Une étude prospective, randomisée, en 2 groupes parallèles ayant pour objectif de comparer la stimulation BIV épicaudique conventionnelle et la stimulation endocardique VG sur des critères hémodynamiques aigus, cliniques et échocardiographiques à 6 mois devrait débuter prochainement (<http://www.clinicaltrials.gov/ct2/show/NCT01260402?term=epi-endo&rank=1>). Par ailleurs, les systèmes miniaturisés de stimulation sans sondes actuellement testés en stimulation conventionnelle VD, devraient permettre le développement de la stimulation endocardique VG à plus large échelle.

13.2 LA STIMULATION MULTIPPOINTS

13.2.1 Rationnel

Deux hypothèses sous-tendent la supériorité potentielle de la stimulation multi-points sur la stimulation BIV conventionnelle. D'une part la probabilité accrue de stimuler au site optimal. D'autre part, la possibilité d'accroître les performances hémodynamiques en réduisant le temps d'activation VG (activation plus physiologique).

13.2.2 Aspects techniques

Chez l'homme, l'expérience se limite à l'usage de 3 sondes ventriculaires (VD ou VG). De façon alternative il est possible de stimuler plusieurs points en ligne sur une sonde quadripolaire dédiée.⁸⁸ Une limitation majeure cependant est la capacité de la batterie du stimulateur, incapable de d'alimenter plus de 4 canaux sur le long terme (en particulier avec des impédances de stimulation basse).

13.2.3 Niveau de preuve

Chez l'animal, nous avons démontré que la stimulation multipoints, en comparaison de la stimulation mono-VG, permettait d'améliorer l'hémodynamique VG, de réduire le temps

d'activation et la dispersion de la repolarisation VG. Nos résultats semblaient indiquer que l'amélioration hémodynamique observée était indépendante de l'effet de resynchronisation cardiaque. Chez l'homme, il semble que la stimulation tri-ventriculaire soit hémodynamiquement supérieure à la stimulation BIV.^{70,89,90} Un premier essai randomisé a comparé la stimulation tri-ventriculaire (2 sondes VG, une VD) à la stimulation BIV chez 34 patients en fibrillation atriale.⁷¹ Après 3 mois de stimulation BIV ou tri-ventriculaire (cross-over), il n'y avait pas de différence entre les deux groupes sur les paramètres cliniques ni en termes de resynchronisation mécanique (Z-ratio), en revanche on observait une réduction des volumes ventriculaires gauches. A noter que dans cette étude la durée du QRS était significativement plus longue en configuration tri-ventriculaire. Un autre essai ayant inclus 18 patients a conclu à des résultats similaires.⁷² L'étude Vcube a explorée le bénéfice de la stimulation tri-ventriculaire (rajout d'une sonde VG) chez le non-répondeur à la stimulation BIV. Les résultats de cette étude sont négatifs tant cliniquement (Packer score) qu'échographiquement (remodelage VG).

13.2.4Limites & perspectives

Bien que séduisante dans son concept la stimulation multi-points souffre de limitations techniques et d'un faible niveau de preuve qui limite son développement en clinique. Là aussi, les capsules stimulantes pourraient jouer un rôle à l'avenir en s'affranchissant des sondes et des problèmes de batterie unique. De plus amples essais contrôlés devraient par ailleurs venir préciser le bénéfice de stratégie.

Positive hemodynamic and clinical response to tri-left ventricular pacing in a nonresponder to traditional cardiac resynchronization therapy

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Multisite left ventricular (LV) pacing is technically challenging, but may result in clinical improvement in patients who do not derive hemodynamic benefit from traditional biventricular pacing.^{1,2} We present the case of a patient who had an implantable cardioverter-defibrillator (ICD) implanted, with 3 epicardial LV leads, in addition to an epicardially placed ICD lead.

A 65-year-old man with severe idiopathic cardiomyopathy was referred to our center after his biventricular ICD became infected. Eight years before this admission he had a dual-chamber ICD implanted from the right side after an episode of sustained ventricular tachycardia. The right-sided system was extracted 6 years later because of lead endocarditis. He subsequently had a biventricular ICD implanted from the other (left) side because he had symptomatic heart failure (New York Heart Association class III), an LV ejection fraction of 25%, complete left bundle branch block, and first-degree atrioventricular block. The LV lead was positioned in a posterolateral vein. He did not gain any symptomatic or echocardiographic improvement in LV function after this procedure, but did receive an appropriate ICD shock during an episode of ventricular tachycardia. He was referred to our center because he developed a second episode of lead endocarditis. Transesophageal echocardiography demonstrated presence of a vegetation on the RV lead.

This raised a challenging clinical question of how to approach the further management of this patient who had received appropriate shocks for ventricular tachycardia, but had developed infection of his ICD lead on 2 occasions. He had severe heart failure and left bundle branch block, but had not noticed a clinical improvement with conventional cardiac resynchronization therapy (CRT). The options for venous access were limited given the previous right- and

left-side implantations. Venography on the left side demonstrated a subclavian vein stenosis.

We proceeded with complete system extraction using the Excimer Laser sheath (Spectranetics, Colorado Springs, Colorado) for the lead extractions. A sternotomy was then performed, and a double-coil ICD lead was directly sutured to the myocardium. The proximal coil was attached to the lateral wall of the right ventricle (RV), and the distal coil was secured to the lateral LV wall (Fig. 1A). No RV site was associated with an adequate sensing threshold. Three LV epicardial leads were then positioned on the posterolateral (LV1), lateral (LV2), and anterior (LV3) walls, respectively. These positions were chosen because they resulted in good spatial separation of the leads across the LV. The sensing and pacing thresholds were acceptable with the leads in this position. One LV lead was connected to the RV port, and the other 2 LV leads were attached to the LV port with the use of a Y connector.

Ventricular fibrillation was induced; this was appropriately detected, and the device delivered a successful 10-J shock. Figure 1B shows the X-ray positions of the ICD and 3 LV pacing leads. Three days after implantation, a Radi pressure wire (St. Jude Medical) was positioned inside the LV cavity via the radial artery to invasively measure the LV dp/dt_{max} . We compared hemodynamic measurement during LV1 pacing, LV2 pacing, LV3 pacing, and tri-ventricular pacing (LV1 + LV2 + LV3 pacing) with 5 atrioventricular sensed delays (80, 100, 120, 150, and 180 ms). None of the possible configurations of mono-LV pacing was associated with hemodynamic improvement compared to baseline. In contrast, tri-ventricular pacing was associated with important hemodynamic improvement compared to baseline (920 vs. 1,104 mm Hg/s). Electrocardiographic imaging was carried out using the Cardioinsight system during baseline, LV pacing, and tri-LV pacing.³ At baseline, we observed the typical activation pattern associated with left bundle branch block (Fig. 2). There was early activation at the level of the anterior RV wall and late activation at the level of the LV apex and the posterolateral LV wall. During LV1 pacing (posterolateral lead), fusion with intrinsic activation was precluded by the first-degree atrioventricular block. The activation was

KEYWORDS Cardiac resynchronization therapy; Nonresponse; Surgery

ABBREVIATIONS CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; LV = left ventricle/ventricular; RV = right ventricle/ventricular (Heart Rhythm 2011;8:315–317)

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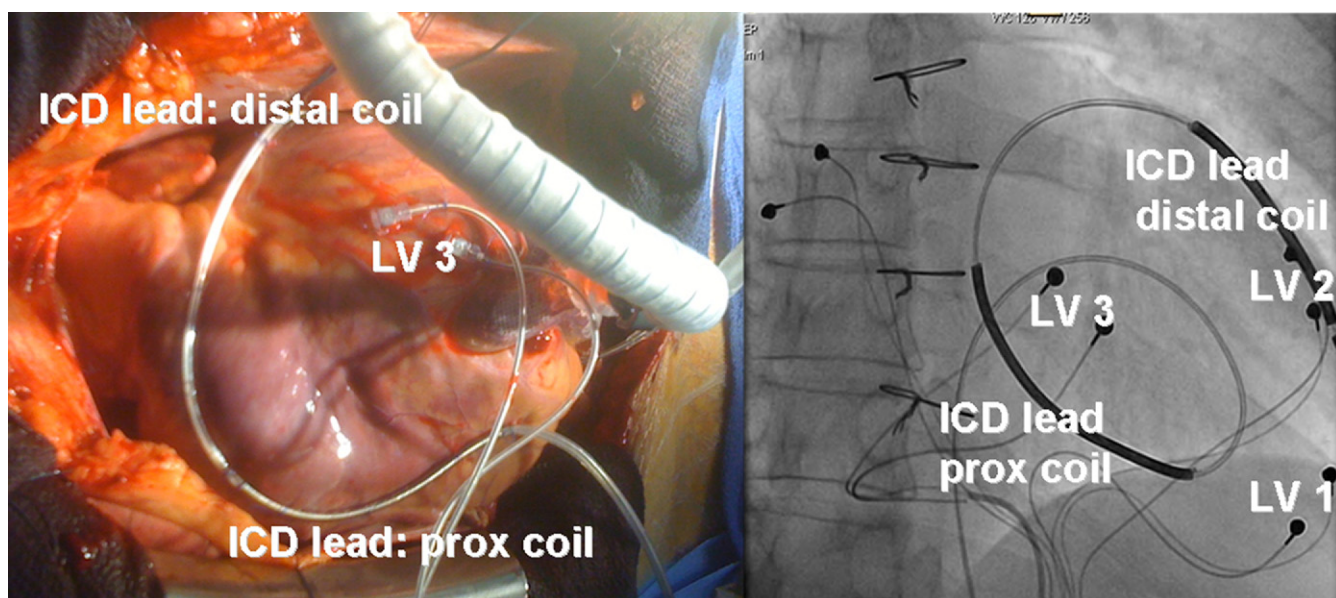


Figure 1 A: Distal coil was secured to the lateral LV wall. B: The X-ray positions of the ICD and 3 LV pacing leads. ICD = implantable cardioverter defibrillator; LV = left ventricle.

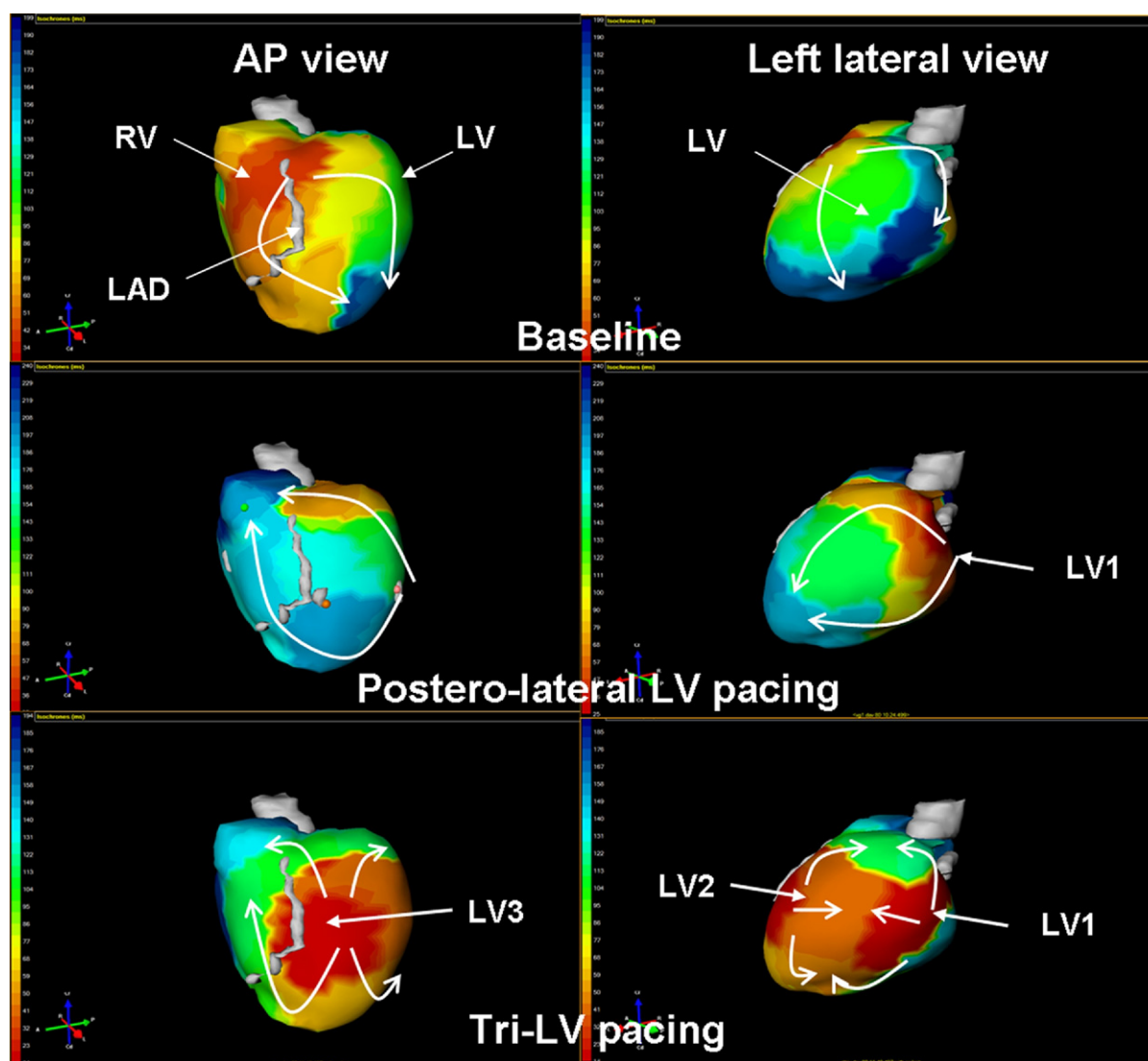


Figure 2 Typical activation pattern associated with left bundle branch block.

reversed with clear early activation at the level of the pacing lead but with areas of late activation at the level of the LV apex, LV anterior wall, and RV cavity. During tri-LV pacing, the spread of activation could be seen to initiate from each of the pacing leads and no areas of late activation in the LV cavity were detected. There was a significant reduction in electrical LV dyssynchrony. The total LV activation time was not reduced during LV1 pacing (134 ms) compared with baseline (141 ms), but was markedly reduced during tri-LV pacing (86 ms). After 10 months of tri-LV pacing, the patient noticed a clear reduction in his heart failure symptoms. His New York Heart Association class improved from III to II. He was considered as an echocardiographic responder with a 17% decrease in end-systolic LV volume (from 142 to 118 ml).

Different small studies have demonstrated a potential interest of implanting 2 LV leads.^{1,4} This case report sug-

gests that in patients with a poor response to traditional (single LV lead) biventricular pacing, multi-LV pacing may provide a solution. When transvenous options are limited, direct suture of an ICD lead to the myocardium is a feasible alternative.

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Left Ventricular Endocardial Pacing and Multisite Pacing to Improve CRT Response

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Received: 3 October 2011 / Accepted: 12 December 2011 / Published online: 11 January 2012
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Abstract Cardiac resynchronization therapy (CRT) is an established treatment for patients with moderate-to-severe heart failure and a wide QRS complex. However, the amount of reverse remodeling and clinical improvement is highly variable and poorly predictable. The left ventricular pacing site is of critical importance for the CRT response but is often imposed by the coronary sinus anatomical constraints and may result in suboptimal resynchronization. Alternative pacing sites, such as endocardial LV pacing or multisite pacing, have been proposed to improve CRT response rates and may be considered in nonresponders to standard resynchronization. However, adequately powered randomized studies are required to determine whether these pacing strategies result in improved outcome.

Keywords Cardiac resynchronization therapy · Heart failure · Endocardial pacing · Nonresponse

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with symptomatic heart failure, severely impaired left ventricular (LV) function, and conduction disorders [1, 2]. Large randomized trials have demonstrated that CRT improves quality of life, symptoms, and reduces heart failure related hospitalizations as well as mortality. However,

about 30% of patients implanted with a single LV lead positioned via the coronary sinus (CS) appear not to respond to CRT. To improve response rate, most attention has been focused on the criteria for patient selection and subsequent optimization of the device settings. However, these strategies have produced mixed results and there have been renewed efforts aimed at optimizing therapy delivery. In that perspective, two new pacing strategies have been proposed to improve CRT response: LV endocardial stimulation and multisite epicardial pacing. In this review, we discuss the rationale, the related technical issues, the potential benefits and the disadvantages of these two promising concepts.

Left Ventricular Endocardial Pacing

Rationale

Endocardial LV pacing appears to provide a more physiological electrical activation of the left ventricle, with the activation spreading from the endocardium to the epicardium. Potentially, this may lower the risk of pacing-induced ventricular arrhythmia. Compared with endocardial pacing, epicardial stimulation increases the transmural dispersion of repolarization and therefore increases susceptibility to re-entrant arrhythmias [3, 4].

LV endocardial stimulation allows greater choice of the pacing site (including the LV septum) with possibility to screen different pacing locations in an attempt to determine the position which results in the greatest improvement in cardiac function. Additional benefits of the endocardial approach may include a better capture threshold and a lower frequency of phrenic nerve stimulation, compared with CS stimulation [5].

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Technical Aspects

Transseptal Approach

The placement of a transseptal LV lead requires the puncture of the interatrial septum to allow the passage of the lead before entering the LV through the mitral valve. Jaïs et al. described, in 1998, the first case of permanent transseptal LV stimulation using a mixed right internal jugular and femoral approach [6]. With the development of dedicated tools, it is becoming increasingly feasible to use a purely superior approach. The transseptal puncture is performed from the superior vena cava using a deflectable sheath to reach the interatrial septum. A guide wire is advanced to the fossa ovalis and radiofrequency energy is applied to allow passage of the wire into the left atrium. The lead is then passed into the LV and positioned through a dedicated inner sheath. The results published regarding the success and complication rates are encouraging [7–10].

A number of potential limitations need to be considered. (1) The risk of thrombus formation on the lead is a major concern with LV endocardial leads. Even small emboli may cause major systemic complications including stroke. The relatively small number of patients who were implanted with an endocardial LV lead received heparin during the procedure and systemic anticoagulation therapy in the long term. This seems to be essential as three cases of thromboembolic event have been reported after improper anticoagulation [8, 11, 12]. (2) An LV lead implanted through the interatrial septum crosses the mitral valve and may increase the risk of regurgitation and endocarditis. Though, to date, the few studies performed have not demonstrated an increase in the grade of mitral regurgitation. (3) Finally, considering the risk of systemic embolization, percutaneous lead extraction in the case of lead infection would be too risky and surgical intervention is likely to be preferred.

Transapical Approach

Hungarian investigators have recently described transapical LV endocardial stimulation through a limited thoracotomy [13]. This strategy shares the same risks as the transseptal approach except for the mitral valve regurgitation. The long term safety and efficacy are still unknown.

Leadless Systems

Leadless pacing may considerably change the reluctance of the physicians to perform LV endocardial pacing. Whatever the technology used, the endocardial electrode would reduce or suppress the risks of thromboembolic complications and the complications associated with the interaction between the lead and the mitral valve [14, 15].

Evidences

Recent animal studies showed a highly significant superiority of LV endocardial pacing compared with epicardial stimulation [16–18]. In eight dogs with acute LBBB, van Deursen et al. compared the hemodynamic and electrophysiological effects of endocardial LV pacing with epicardial LV pacing at eight different sites. (1) LV endocardial pacing was associated with a significant decrease in LV total activation time as compared to LV epicardial pacing. (2) Biventricular pacing with LV endocardial stimulation also decreased the dispersion of repolarization. This suggests that endocardial stimulation is more physiological and may be less arrhythmogenic than conventional CRT. (3) In addition, endocardial pacing increased the benefit on LVdP/dtmax and stroke work by 90% and 50%, respectively, when compared to epicardial pacing at the same site.

Using a similar protocol, Strik et al. compared endocardial biventricular pacing and epicardial biventricular pacing in dogs with acute LBBB, in dogs with chronic LBBB associated with myocardial infarction, and in dogs with chronic LBBB and tachy-pacing-induced heart failure. They demonstrated unequivocally the superiority of endocardial over epicardial stimulation on hemodynamic measurements and on the decrease in LV activation time. The electric resynchronization was greater in hearts with concentric (ischemic model) than with eccentric remodeling (dilated cardiomyopathy) [17].

We have recently presented the results of an acute hemodynamic study of endocardial pacing in patients with heart failure [19]. In 35 patients with non-ischemic cardiomyopathy, we have compared the hemodynamic effect of 10 endocardial and one epicardial pacing sites. The optimal endocardial pacing site allowed a doubling of the hemodynamic (dP/dtmax) benefits compared with the standard epicardial stimulation of the LV free wall. It is noteworthy that the comparison between epicardial and endocardial stimulation at the same site did not show any significant difference in dP/dtmax. Similar observations were made by Spragg et al. in 11 ischemic heart failure patients suggesting that the maximal enhanced response seen with endocardial stimulation (compared to a conventional lateral epicardial site) was more likely to be due to accessing ideal LV pacing sites rather than to endocardial stimulation per se [20].

Comparing endocardial LV pacing at four different sites and epicardial LV pacing in a lateral tributary of the coronary sinus, Ginks et al. found in 15 heart failure patients that the best LV endocardial site provided a higher improvement in dP/dtmax than the coronary sinus site while the left ventricular endocardial activation time did not change between the two pacing configurations [21].

Currently, there are few studies with longer-term follow up. Garrigue et al. compared 15 heart failure patients implanted with a conventional CRT system with eight patients stimulated

with transseptal LV leads [22]. At 6 months, patients implanted with a LV endocardial lead showed less ventricular dyssynchrony, greater LV shortening fraction and a higher mitral velocity-time integral.

In conclusion, endocardial LV pacing may be a promising alternative to lower the proportion of nonresponders to epicardial LV resynchronization. The implementation of endocardial stimulation will ultimately depend on (1) the development of (a) an instrumentation that is safe and effective on the long term and (b) reliable and reproducible methods to identify the optimal site of stimulation during the procedure, and (2) the completion of controlled trials confirming the superiority of this technique compared to standard CRT.

Multisite Pacing

Rationale

The potential benefit of a multiventricular pacing approach may involve two different mechanisms. First, by increasing the number of pacing sites, the probability of reaching a more efficient site may be increased. Endocardial mapping studies confirm that the substrate which we seek to treat with CRT is diverse, complex, and displays significant interpatient variation [21, 23, 24]. Changing left ventricular pacing site has been shown to influence the ventricular activation sequence and the hemodynamic response. Ventricular activation is dependent on multiple factors including proximity to scar and areas of slow conduction, etiology of heart failure, and conduction system disease [25–27]. Secondly, one can hypothesize that more spots of activation will provide a faster and more physiological LV activation (Fig. 1) [28, 29].

Technical Aspects

Multiventricular pacing can be achieved by the addition of one or two ventricular leads (RV or LV) to a traditional CRT system (RV+LV). In the Triple Resynchronization in Paced Heart Failure Patients (TRIP-HF) study, the success rate of implantation of two LV leads was 85% with a mean duration of implant procedure of 2.03 ± 0.97 h. During the 9 months of follow-up, five of 34 patients had phrenic nerve stimulation, four required lead repositioning, and two patients underwent explantation due to infection suggesting a quite high level of complications [30].

Instead of using two or more different leads, it would be technically easier to pace from two or more electrodes inline on the same epicardial LV lead. A quadripolar pacing lead has been developed to provide delivery of pacing stimuli using any of the four electrodes as the cathode with the RV ring as the anode. It is also possible to provide bi-LV pacing using two different LV electrodes at the same time [31]. Concerning the question of the

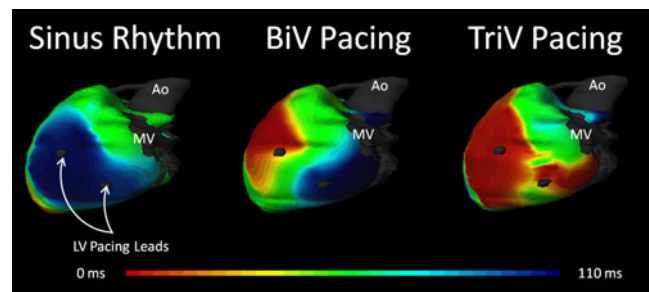


Fig. 1 Electrocardiographic imaging maps (epicardial non-invasive mapping) during spontaneous rhythm, biventricular and triventricular pacing in a patient with left bundle branch block implanted with two LV leads. In sinus rhythm, the latest activation is observed at the LV lateral wall. During biventricular pacing, this region is activated by a wavefront propagating from the midlateral LV whereas the posterolateral area is still delayed. During triventricular pacing, we observed a faster activation of the whole left ventricle with a substantial decrease in dyssynchrony

potential interest of this lead to improve the response after CRT, the major question is to compare the respective impact of bi-left ventricular pacing with the two electrodes in the same vein or with the two electrodes in different veins.

Surgical epicardial LV lead implantation has also been proposed to increase the number of pacing sites. This can be achieved via left anterior or lateral minithoracotomy, video-assisted thoracoscopy, and robotically enhanced telemanipulation systems [32].

Whatever the operative strategy, the number of pacing sites is limited by the currently available pacemaker which can only provide three pacing channels (Atrial, RV, LV). Two leads can be connected to the same port using a parallel Y-connector with a drop in impedance and an increase in power consumption. So far, there have been no reports of multisite endocardial LV pacing; a leadless pacing system would be preferably for that purpose.

Evidence

Multi RV Pacing

Yoshida et al. described the case of a patient who did not respond after traditional CRT but who did improve after the implantation of a second RV lead positioned in the outflow tract [33]. In a larger study, they observed a significant improvement in acute dP/dt_{max} and cardiac output as well as an improvement in dyssynchrony comparing in 21 heart failure patients traditional biventricular pacing and triventricular pacing (one LV lead and two RV leads) [34]. The largest hemodynamic improvement provided by triventricular pacing was observed in patients with a large LV end-diastolic volume [35].

Multisite LV Pacing

Implanting a second LV lead has been reported to improve the hemodynamic and/or the outcome of nonresponders to

conventional CRT [32, 36]. In 14 heart failure patients with a basal QRS duration ≥ 150 ms, Pappone et al. found that dual-LV pacing increased dP/dtmax significantly more than posterior base and lateral wall pacing alone [37]. Conversely, Padeletti et al. did not find additional value with dual-LV pacing when the single LV pacing site and atrioventricular interval were optimal [38]. Peschar et al. did not observe any benefit in terms of dP/dtmax and stroke work of multiLV pacing (i.e. LV apex, LV anterior, LV lateral, and LV posterior wall) as compared to LV apex alone in 11 healthy (without conduction disturbance) dogs [39].

In a retrospective nonrandomized trial, Lenarczyk et al. have compared 27 patients implanted with 2 LV leads and 1 RV lead (TriV) with 27 patients receiving a biventricular pacing system. After 3 months of CRT, TriV pacing was associated with a significant reduction in New York Heart Association class (by 1.4 vs. 1.0 class, respectively), increase in VO₂ max (2.9 vs. 1.1 mL/kg/min) and 6-min walk distance (98.7 vs. 51.6 m) compared with conventional biventricular pacing [40].

TRIP-HF was the only prospective, randomized study comparing the effects of triple-site (TriV) versus dual site biventricular stimulation (BiV) [30]. Forty patients with moderate-to-severe heart failure in permanent atrial fibrillation were enrolled and 34 of them were successfully implanted with one RV lead and two LV leads. After a run-in period of 3 months of biventricular pacing, the patients were randomly assigned to either 3 months of TriV followed by 3 months of BiV or the other way round (cross over). At 3 months, the distance covered during a 6-min test and the quality of life scores were not different between the two groups. However, triventricular pacing conferred a significant improvement in LVEF and LVESV over biventricular pacing.

The ongoing V3 Trial is specifically design to answer the question of whether the addition of a second LV lead may improve the outcome of nonresponders [41]. A total of 84 traditional CRT nonresponders will be enrolled in 11 different medical centers. Half of the patients will be randomly assigned to receive an additional LV lead, the other half will keep the pacing system unchanged (control). The Packer's classification will be used to compare the two groups (BiV versus TriV) at 12 months as a primary endpoint. Secondary end points will include change of quality of life, exercise capacity, number of hospitalizations or death, echocardiographic indices of LV remodeling and blood levels of N-terminal pro-B natriuretic peptide.

Conclusion

CRT is an established treatment for patients with moderate-to-severe HF and a wide QRS complex. However, the amount of reverse remodeling and clinical improvement is

highly variable and poorly predictable. Optimal pacing position is highly variable among patient but the site of pacing is often imposed by the coronary sinus anatomical constraints. Alternative pacing sites, such as endocardial LV pacing or multisite pacing, have been proposed to improve CRT response rates and may be considered in nonresponders to standard resynchronization. However, further larger randomized and long-term studies are needed to confirm the potential benefits and the safety of these new pacing strategies.

Funding Dr. Ploux is supported by a grant from the French Federation of Cardiology.

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SYNTHESE ET PERSPECTIVES

15 SYNTHÈSE ET PERSPECTIVES

Les différentes études réalisées dans le cadre de cette thèse ont abouti aux conclusions suivantes : 1) les patients avec BBG représentent la cible privilégiée de cette thérapeutique du fait d'une séquence d'activation asynchrone caractéristique avec un élément déterminant, l'existence d'un retard d'activation relatif du ventricule gauche par rapport au ventricule droit (VEU) qui peut être corrigé par la resynchronisation BIV ou inversé par une stimulation mono VG 2) à l'inverse, le taux de réponse favorable après resynchronisation chez les patients avec QRS fins est extrêmement faible, la stimulation ayant tendance au contraire à créer une désynchronisation et une séquence d'activation délétère 3) les patients avec bloc indifférencié (NICD) représentent une population intermédiaire ; si il est possible de caractériser la séquence d'activation d'un BBG ou d'un QRS fin, nous n'avons pas retrouvé de séquence d'activation-type dans le cadre du bloc indifférencié. Ces différences d'activation expliquent des variations interindividuelles importantes en termes de réponse après resynchronisation 4) si il existe des similitudes en termes de séquence d'activation chez un patient avec bloc de branche gauche et un patient stimulé à l'apex du ventricule droit, il existe également des différences pouvant expliquer une probabilité moindre de réponse après resynchronisation dans le cadre d'un rajout de sonde ventriculaire gauche chez le patient préalablement stimulé 5) la cartographie non invasive plus ou moins couplées à des données provenant d'un modèle informatique d'insuffisance cardiaque avec asynchronisme permettent de mieux appréhender les mécanismes impliqués dans la resynchronisation et pourraient dans le futur permettre d'optimiser la sélection des candidats à la resynchronisation ainsi que le choix des différents sites de stimulation 6) la stimulation multipoints, difficile à implémenter aujourd'hui en pratique clinique en raison de limites technologiques, est une option séduisante à évaluer dans le futur pour améliorer le degré de réponse à cette thérapeutique.

15.1 BLOC DE BRANCHE GAUCHE, DECOUPLAGE D'ACTIVATION VENTRICULAIRE,

REPONSE FAVORABLE A LA RESYNCHRONISATION, MECANISMES IMPLIQUES

Il existe peu d'études portant sur l'analyse de la séquence d'activation électrique observée dans le cadre du BBG chez le patient insuffisant cardiaque.^{43-45,91} Nous avons réalisé une étude cartographique électrocardiographique épicaudique chez un nombre important de patients insuffisants cardiaques présentant différents degrés d'asynchronisme, de largeur et d'aspect du QRS. Quand on replace le BBG dans le cadre du large spectre des troubles de conduction observés chez les patients insuffisants cardiaques, il apparaît que ces patients avec BBG présentent une séquence d'activation très caractéristique avec beaucoup plus de points communs entre les patients que de différences. L'activation ventriculaire propre au BBG est facilement identifiable et très différente de celle observée chez les patients avec QRS fins : activation ventriculaire droite rapide, absence de primo activation ventriculaire gauche, activation du ventricule gauche à partir du ventricule droit selon deux fronts parallèles au grand axe cardiaque, présence d'une à quatre lignes de conduction lente orientées de la base vers l'apex, paroi la plus retardée systématiquement située dans la région basolatérale ventriculaire gauche. Ayant un profil d'activation homogène, ces patients avec BBG répondent globalement favorablement et uniformément à la stimulation BIV. De façon intéressante, une analyse détaillée du substrat de base par cartographie électrocardiographique permet de prédire la réponse clinique à moyen terme avec plus d'acuité que l'électrocardiogramme de surface. Une composante essentielle de ce substrat, représentant probablement la cible préférentielle de la resynchronisation, est le retard d'activation relatif du ventricule gauche par rapport au ventricule droit (VEU). Quand il dépasse un degré minimal d'environ 50ms, il traduit l'existence d'un découplage d'activation ventriculaire qui se traduit par une perte de la contribution de la paroi septale au travail cardiaque global. La paroi septale, habituellement déterminante dans le fonctionnement de la pompe cardiaque et dans l'interdépendance entre la contraction des 2 ventricules, présente dans le cadre du BBG, une contraction déphasée, altérée et parfois même opposée à celle des autres parois.^{6,60,92}

Chez les patients avec BBG, stimulation BIV et stimulation mono-VG induisent un bénéfice hémodynamique et clinique similaires avec pourtant des différences marquées en termes de mécanismes impliqués. La stimulation BIV permet de réduire les différents niveaux d'asynchronisme, ramenant le VEU à l'équilibre et réduisant le temps d'activation VG. A l'opposé, l'effet positif observé après stimulation mono-VG se produit sans réduction des degrés d'asynchronisme ventriculaire. La séquence d'activation lors d'une stimulation mono-VG est inversée par rapport à celle observée lors d'un BBG, les valeurs absolues de VEU n'étant pas significativement modifiées. Le terme « resynchronisation » ne semble donc pas adéquat pour une thérapie basée sur une stimulation mono-VG. Le bénéfice observé sur la fonction cardiaque globale tient à l'augmentation de la participation du ventricule droit au travail cardiaque. Il paraît donc logique d'attendre, chez un patient donné, une réponse variable selon le mode de stimulation (BIV ou mono-VG) en fonction des capacités contractiles intrinsèques de chaque ventricule. Cette hypothèse fera l'objet d'un travail couplant données expérimentales et données provenant du modèle informatique qui débutera prochainement dans le service.

15.2 QRS fins, NOTION DE DESYNCHRONISATION ET ASYNCHRONISME POST-

« RESYNCHRONISATION »

Les résultats observés chez les patients avec QRS fins se sont avérés décevants. A l'opposé de certaines données publiées, nous n'avons pas retrouvé de bénéfice hémodynamique après resynchronisation et surtout nous n'avons pas pu mettre en évidence l'existence d'un potentiel sous-groupe de patients avec QRS fins répondant favorablement. Ces résultats sont conformes aux conclusions des études randomisées, à la méthodologie non discutable, montrant un effet nul voire négatif de la resynchronisation chez ces patients.^{65,66,93} Nous avons démontré qu'il existe une corrélation forte entre asynchronisme électrique, évalué par la durée du QRS de surface ou plus précisément par des paramètres dérivés de la cartographie électrocardiographique, et réponse hémodynamique après stimulation BIV. Les patients avec QRS fins présentent des temps d'activation subnormaux avec participation active de tout ou partie du réseau de Purkinje à la dépolarisation ventriculaire. Aucun de ces patients ne présente un VEU significativement altéré et dépassant le seuil de 50 ms. La stimulation BIV a pour effet

de ramener le VEU proche de zéro quel que soit le substrat sur lequel elle est appliquée. La stimulation BIV entraîne également une activation des deux ventricules indépendante du système de conduction spécialisé, avec des valeurs de TAT et LVTAT peu variables en fonction du substrat (conduction musculaire de cellule à cellule). Les patients répondeurs présentent un raccourcissement de leurs temps d'activation par la stimulation BIV (ceci suppose un degré d'asynchronisme de base supérieur, sous-entendant une activation intrinsèque musculaire), alors que les non-répondeurs présentent un allongement de ces temps (perte de la conduction médiée par le réseau de His-Purkinje). L'allongement des temps d'activation total et VG va de pair avec une détérioration de l'hémodynamique cardiaque et peut-être du pronostic. L'induction d'une électropathie par la stimulation BIV est une entité méconnue qu'il faut impérativement prévenir par une analyse appropriée du substrat des candidats à la stimulation BIV. Nous avons montré que les patients à QRS fin ne présentaient pas d'asynchronisme suffisant et qu'ils étaient donc susceptibles à l'asynchronisme induit par la stimulation BIV. Cette observation pourrait constituer une base physiopathologique à l'aggravation du pronostic de ces patients décrit par la stimulation BIV. En fait, il est probable que tous les patients présentant une activation intrinsèque VG via le réseau de Purkinje puissent souffrir d'une prolongation du temps d'activation VG induit par la stimulation BIV. Ainsi la stimulation BIV corrige le VEU mais est loin d'offrir une activation ventriculaire normale, elle induit un nouvel état d'asynchronisme avec majoration des temps d'activation ventriculaire droit et gauche par rapport à la normale.

15.3 BLOC INDIFFERENCIÉ

La technique de cartographie ECM a permis de mieux appréhender les différences en termes d'activation observées chez les patients avec bloc indifférencié expliquant des résultats disparates après resynchronisation. L'appellation bloc indifférencié regroupe les différents cas où la durée de QRS est allongée au-delà de 120 ms sans qu'il n'y ait un aspect de BBG ou de bloc de branche droit clairement identifiable. Il s'agit donc d'une définition par défaut. Il existe différentes raisons d'observer un QRS large sans l'aspect typique de bloc de branche : soit le patient présente une lésion réelle d'une branche mais l'aspect électrocardiographique est

atypique en raison par exemple de la superposition des signes électriques d'une lésion pariétale, soit les voies de conduction sont intactes mais la durée de l'activation est prolongée en raison d'un retard myocardique local ou plus global de la propagation de l'influx.

Dans le sous-groupe de bloc indifférencié, il faut inclure l'aspect de *bloc de branche gauche atypique* observé dans le post-infarctus correspondant à l'existence probable d'un BBG réel, la superposition du trou électrique en rapport avec la nécrose modifiant l'aspect typique électrocardiographique. L'électrocardiogramme met en évidence la présence d'ondes Q larges et profondes dans plusieurs dérivations suite à un infarctus du myocarde étendu ou touchant plusieurs territoires avec un aspect de retard gauche. La séquence d'activation de ce type de patients devrait se rapprocher de celle observée chez les patients avec bloc de branche gauche typique. A l'opposé, on retrouve dans le sous-groupe des blocs indifférenciés, des patients avec un complexe QRS élargi au-delà de 120ms, qui conserve un aspect d'ensemble non ou peu modifié. Il peut s'agir de bloc de conduction distaux sur le réseau de Purkinje, intra-myocardique, ou encore d'un élargissement en rapport avec une hypertrophie myocardique. En résumé, ces différents sous-groupes de patients avec bloc indifférencié présentent un point commun (QRS large sans aspect typique de bloc droit ou gauche) mais correspondent à des entités cliniques et physiopathologiques très diverses allant de l'existence de blocs tronculaires de conduction réels mais à l'aspect électrocardiographiques atypiques à une conduction tronculaire préservée avec altération de l'activation distale plus ou moins étendue.

Ainsi s'il est possible de définir une activation électrique relativement stéréotypée et homogène dans le BBG, il paraît illusoire d'imaginer une séquence d'activation standard caractéristique pour les blocs indifférenciés permettant d'envisager une réponse homogène après resynchronisation dans ce sous-groupe de patients. Les résultats observés dans la littérature confirment l'existence de résultats parfois contradictoires après resynchronisation dans ce sous-groupe. Il n'existe pas à ce jour d'études randomisées dédiée aux patients avec bloc indifférencié, les données existantes correspondant à des analyses en sous-groupe. La pertinence des analyses en sous-groupes est débattue et le nombre limité de patients inclus ne permet pas de tirer des conclusions définitives. Une méta-analyse récente suggère que la resynchronisation aurait un effet neutre chez les patients avec bloc indifférencié, alors que dans

l'étude MADIT-CRT prolongée sur 7 ans, la resynchronisation semble aggraver la mortalité de ces patients.^{26,27,67} Ces résultats, même si il existe un certain nombre de limites (faibles effectifs, analyse en sous-groupe), ont entraîné des modifications notables dans les dernières recommandations internationales, l'aspect du QRS et plus seulement la largeur du QRS devenant un critère de sélection des candidats à la resynchronisation.⁶¹

La question qui se pose aujourd'hui est de savoir s'il est encore opportun d'implanter ces patients. Les études réalisées au cours de ce travail ont permis d'objectiver une diversité importante en termes de séquence d'activation dans ce sous-groupe de patients et en corollaire de démontrer la variabilité dans la réponse hémodynamique et clinique après resynchronisation. Les patients avec bloc indifférencié présentaient un temps d'activation ventriculaire gauche (91 ± 34 ms vs. 115 ± 21 ms; $p < 0.03$) et un VEU (40 ± 22 ms vs. 75 ± 12 ms; $p < 0.001$) moindres que ceux avec bloc de branche gauche. Nous avons mis en évidence un large spectre de séquence d'activation avec pour certains un aspect proche de celui observé chez les patients avec QRS fins (peu d'asynchronisme, trouble de conduction diffus et/ou localisé) présentant une faible probabilité de réponse favorable à la resynchronisation et pour d'autres un aspect proche de celui du bloc de branche gauche (VEU significatif), potentiels bons candidats à la resynchronisation. De façon intéressante, le critère du VEU permettait de mieux identifier la réponse à la CRT que la largeur du QRS ou son aspect (bloc de branche gauche *versus* bloc indifférencié). Une valeur de VEU supérieure à 50 ms était observée chez 20% des patients avec bloc indifférencié; ces patients se sont avérés bons répondeurs à la resynchronisation.

Il existe donc probablement un sous-groupe de patients avec bloc indifférencié susceptibles de répondre favorablement à la resynchronisation. Ces résultats ont besoin d'être confirmés sur des effectifs plus importants. Il est possible d'envisager dans ce cadre différentes études dédiées à ce sous-groupe de patients insuffisants cardiaques. Une première étude pourrait inclure uniquement des patients insuffisants cardiaques avec bloc indifférencié et QRS large sans autre critère supplémentaire de sélection (aspect de l'ECG ou paramètres électriques ou échographiques). Au vu du nombre de patients présentant cette anomalie électrocardiographique, il est possible d'envisager une étude randomisée, contrôlée, en aveugle

en 2 bras (resynchronisation *versus* absence de resynchronisation), basée sur des critères de jugement forts type hospitalisation et/ou mortalité. Cette étude permettrait de répondre à la question de l'efficacité de la resynchronisation dans ce sous-groupe de patients mais les résultats préliminaires et la diversité des profils de ces patients laissent plutôt présager d'un résultat négatif. Une seconde option serait d'essayer de trouver dans ce sous-groupe de patients, un sous-groupe susceptible de répondre favorablement à la resynchronisation. La sélection pourrait être basée sur un critère électrique de cartographie (VEU).

15.4 STIMULATION VENTRICULAIRE DROITE VERSUS BLOC DE BRANCHE GAUCHE

En raison d'une séquence d'activation ventriculaire similaire à celle observée dans le BBG, les patients stimulés à l'apex du ventricule droit ont été proposés comme candidats à la stimulation BIV. Notre étude retrouve indiscutablement un certain nombre de caractéristiques communes, la séquence d'activation observée lors d'une stimulation ventriculaire droite apicale étant bien plus proche de celle du bloc de branche gauche que de celle observée chez les patients avec QRS fin par exemple. Nous avons toutefois mis en évidence des spécificités de l'activation induite par la stimulation VD (comme le prolongement de RVTAT) qui suggèrent un comportement différent à la stimulation BIV. Si comme nous le pensons, l'existence d'un VEU significatif représente la cible privilégiée de cette thérapeutique, l'impact de la resynchronisation pourrait être moindre dans le sous-groupe préalablement stimulé dans le ventricule droit (VEU significativement plus court que dans le BBG). La question de la justification de la stratégie d'ajout d'une sonde ventriculaire gauche dans ce sous-groupe de patients ne nous paraît pas devoir être remise en cause aujourd'hui. En effet, même si le bénéfice escompté est possiblement moins important que dans le cadre du bloc de branche gauche, ce bénéfice peut rester significatif, des études supplémentaires sur large effectif dédiées à ce sous-groupe de patients devant être réalisées dans ce cadre.

15.5 CARTOGRAPHIE NON INVASIVE ET MODELE INFORMATIQUE

La sélection des candidats à la resynchronisation est aujourd'hui basée sur la largeur mais également l'aspect du complexe QRS. Quoique rudimentaire, l'électrocardiogramme de surface

reste donc l'outil recommandé par les différentes sociétés internationales parce que simple d'utilisation et de diffusion quasi-universelle et parce que les études successives ont validé l'importance des caractéristiques du QRS dans le degré de réponse après resynchronisation. Le cahier des charges pour une technique visant à supplanter l'électrocardiogramme est donc bien défini : cette technique doit être applicable en pratique courante à large échelle, elle doit être fiable et reproductible et enfin elle doit permettre d'améliorer le rendement de cette thérapeutique particulièrement en réduisant le nombre de patients non répondeurs. La cartographie non invasive pourrait remplir un certain nombre de ces pré-requis. Au cours des études que nous avons réalisées dans le service, nous avons pu confirmer une excellente faisabilité et un degré élevé de reproductibilité. Les évolutions successives du matériel disponible et des différents logiciels d'analyse ont permis de réduire progressivement l'influence respective de l'opérateur dans l'analyse des différentes cartes et la mesure des paramètres d'asynchronisme permettant une reproductibilité intra et inter-opérateurs probablement bien supérieure à celle constatée pour les techniques échographiques d'évaluation basées sur l'analyse du déplacement segmentaire. L'intérêt principal de cette technique tient surtout dans le fait que nos résultats montrent un rendement supérieur par rapport à l'électrocardiogramme de surface. Un exemple réside dans la quantification du VEU, paramètre déterminant pour la prédiction de la réponse, qui ne peut pas être extrait de l'analyse de l'électrocardiogramme 12 dérivations. L'analyse des cartes d'activation pourrait principalement permettre de sélectionner un sous-groupe de patients susceptibles de répondre favorablement dans une population à faible probabilité de réponse positive.

Nous pensons également que cette technique, éventuellement couplée à des données provenant d'un modèle informatique, pourrait permettre d'optimiser le positionnement des sondes de stimulation, une question sans solution à ce jour. Une stratégie basée sur la recherche du site de stimulation optimal à l'aide d'un modèle informatique nourri des données électrophysiologiques propres du patient obtenues par cartographie paraît très séduisante et finalement non utopique ou éloignée dans le temps. En effet, les premiers résultats obtenus avec le modèle semblent extrêmement prometteurs. Les résultats de l'étude Opti-CRT, réalisée dans le service et portant sur l'intérêt des cartes d'activation en salle d'implantation pour définir

le site optimal, devraient nous permettre de mieux comprendre la relation entre substrat anatomique, activation électrique et site de stimulation optimal.

Les limites de la cartographie électrocardiographique non invasives à ce jour sont : la nécessité de réaliser un scanner thoracique, la nécessité d'utiliser une veste multiélectrode complexe, une faible résolution des cartes de voltage enfin sa faible diffusion (utilisation exclusive dans quelques centres de recherche). Récemment nous avons réalisé avec succès chez l'animal une géométrie à l'aide de l'IRM cardiaque qui a permis l'acquisition de cartes d'activation en s'affranchissant de l'exposition aux rayons ionisants. Il sera probablement possible dans un avenir proche d'utiliser la radiographie conventionnelle pour effectuer cette géométrie. De même, il est possible de réduire le nombre d'électrodes de surface qui est actuellement de 250, à moins de 100. L'algorithme de résolution du problème inverse est en perpétuelle amélioration et la quantification du substrat par cartographie de voltage est un axe de recherche privilégié. L'accumulation de preuves scientifiques de l'apport clinique de la cartographie non-invasive implique l'arrivée de fonds d'envergure qui vont permettre sa vulgarisation et sa diffusion.

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